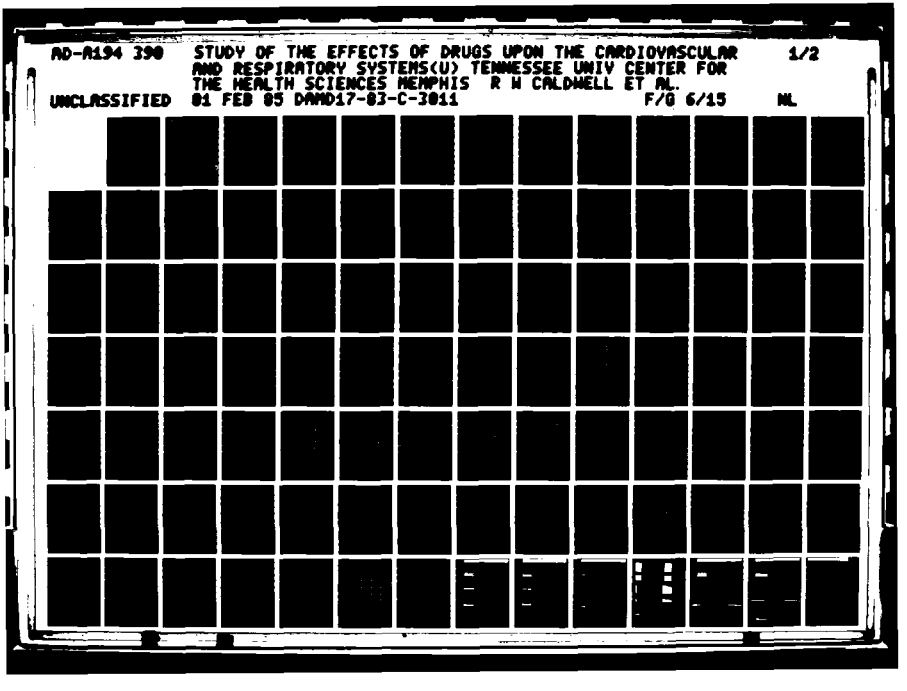
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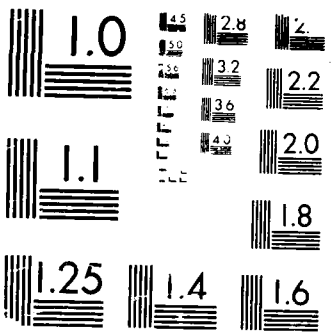

MICROCOPY RESOLUTION TEST CHART

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STUDY OF THE EFFECTS OF DRUGS UPON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

ANNUAL PROGRESS REPORT

by

Robert W. Caldwell

Clinton B. Nash

February 1, 1985

(January 1, 1984 - December 31, 1984)

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

Contract No: DAMD17-83-C-3011

University of Tennessee Center for the Health Sciences
Memphis, Tennessee 38163

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During this past year we have: 1. Completed study of Cardiovascular and Pulmonary Effects of WR-6026-2HCl vs Primaquine Diphosphate. A copy of this report is attached (Section I). 2. Written a protocol to determine the Involvement of Histamine in the Blood Pressure Responses to Liposome Carriers (Section II). 3. Performed preliminary experiments on the Effects of Carrier Liposomes on the Canine Cardiovascular System. A copy of results is attached (Section III).

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Summary

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1. Completed study of Cardiovascular and Pulmonary Effects of WR-6026-2HCl vs Primaquine Diphosphate. A copy of this report is attached (Section I).

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FOREWARD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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SECTION I.

COMPARISON OF CARDIOVASCULAR AND PULMONARY EFFECTS OF WR-6026-2HCl and PRIMAQUINE DIPHOSPHATE

by

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Headquarters, U.S. Army Medical

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Command Office of Surgeon General

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Summary:

A comparison was made of a variety of cardiovascular and pulmonary effects of WR-6026·2HCl and primaquine diphosphate in anesthetized dogs utilizing dose rates which were either only minimally effective in producing changes (1.0 μmoles/kg/min for WR-6026 and 0.5 μmoles/kg/min for primaquine) or those producing marked effects just short of death (4.0 μmoles/kg/min for WR-6026 and 1.75 μmoles/kg/min for primaquine). Cardiopulmonary actions of these two drugs differed. Note that the molar dose range for WR 6026 amounted to approximately twice that for primaquine.

In the cardiovascular system, the predominant effect of primaquine was an increase in pulmonary vascular resistance. A modest depression of cardiac contractility was noted for all dose-rates, but this was evident only at the end of the experimental period. The EKG changes indicated some transient slowing of A-V transmission and ventricular conduction. Although these changes were not prominent, one animal did develop ventricular arrhythmias at the high dose, reverting about 25 minutes later. A 2 μmole/kg/min dose-rate of primaquine caused ventricular arrhythmias and death in one of two dogs tested.

The major effects of WR-6026-2HCl were a weakening of ventricular contractility and a constriction of the pulmonary vasculature. These effects were significant at the middle and high doses, but either did not occur or were unimportant at the low dose. There was some short-lived increase in P-R interval and Q-T interval by the high dose, but no cardiac arrhythmias.

Respiratory rate was transiently raised during high dose-rate infusion of primaquine. Compliance appeared variably affected by the different dose-rates of primaquine.

On the respiratory system, WR-6026 produced immediate elevations of respiratory rate and minute volume at all dose-rates tested. WR-6026 also produced a prominent depression in airways resistance at the higher doses.

The most dangerous effect of WR-6026 is progessive depression of cardiac contractility to the point of ineffective cardiac pumping. In contrast, the potentially lethal action of primaquine is upon cardiac rhythm.

Cardiovascular and Pulmonary Effects of

WR-6026•2HCl vs Primaquine•$2H_3PO_4$

BACKGROUND

During World War II there was a great interest in developing new antimalarial drugs. A very fruitful source of active compounds was found to be the 8-aminoquinolines. Early in the experimental studies of these agents it was noted that they had a wide variety of cardiovascular effects.

WR-6026 is an 8-aminoquinoline originally synthesized in the malarial research program during World War II. However, more recently this substance has been noted to be the most active antileishmanial compound tested in the WRAIR screening program from more than 3000 compounds. Because of structural similarities of WR-6026 to primaquine (see below), one would expect similar cardiopulmonary actions from these two agents. This protocol describes experiments to make such a comparison.

The purpose of these experiments is to compare the effects of intravenous infusions of WR-6026 with those of primaquine upon the rhythm, electrical activity and the function of the heart, the pulmonary blood pressure and circulation, the systemic blood pressure and circulation and the pulmonary ventilation, including blood O_2, CO_2 and pH.

Previous Studies with WR-6026•2HCl (hereafter referred to as WR-6026) -- According to Korte and Basmania (1981), the cardiopulmonary profile of WR-6026, determined following intravenous administration, was unique in that it produced urticaria and angioneurotic edema in the anesthetized dog. This

response was hypothesized to be due to a non-hypersensitive release of endogenous autocoids, such as histamine. The hypotensive effect of bolus injections of WR-6026 and the increase in hematocrit observed during a 45-minute infusion of WR-6026 were consistent with a hypothesis of histamine release. Infusion of WR-6026, 17.8 mg/kg over a 45-minute period, also produced a decrease in heart rate and prolongation of the PR, QTc and QRS intervals of the electrocardiogram similar to that observed with primaquine. WR-6026, like primaquine, may affect reflex sympathetic activity as it blunted the expected increase in pulse pressure and heart rate following carotid occlusion. However, unlike primaquine, WR-6026 did not attenuate the cardiopulmonary responses of isoproterenol.

PRELIMINARY DOSE-RANGING EXPERIMENTS -- In our initial studies with WR-6026 we determined the range of dose-rates of the candidate drug that, in our preparation, produce either: (1) minor but perceptable changes in the cardiopulmonary variables, or (2) the most severe alterations in cardiovascular and pulmonary function short of death. Dogs were anesthetized and prepared as described in the Methods Section outlined later in this report. Following surgical preparation, application of monitoring instruments, and a period for stabilization of cardiopulmonary function, control values were recorded over a 30-minute period followed by intravenous infusion of drug or phosphate buffer vehicle at selected dose rates over a 20-minute period in a total volume of 80 ml.

Dose-rates initially selected for investigation were those, on a molar basis, which in our previous studies of candidate antimalarials produced definite but non-lethal cardiopulmonary effects. We were also guided by

information provided by Dr. Howard Lowensohn of WRAIR. Our results indicated a dose-response curve of similar slope to that previously noted for primaquine (Interim Report No. 6, University of Tennessee, 10 November, 1980).

A. Determination of Maximum Tolerated Dose-rate of WR-6026 -- Successive increases in dose-rate of WR-6026 in anesthetized dogs have demonstrated that 4 μmoles/kg/min is the maximum tolerated dose-rate. An infusion of 6 μmoles/kg/min produced death of both dogs so treated during the 20-minute drug infusion. An example of one of these range-finding experiments is given in TRACINGS 1A,B,C&D. An infusion rate of 5 μmole/kg/min caused death in 3 out of 5 animals. There were progressive decreases in systemic arterial pressure, heart rate, left ventricular dP/dt max. and airway resistance with loss of effective cardiac function and arterial perfusion pressure by the end of the 20-minute period. Respiratory rate, tidal volume, pulmonary wedge and pulmonary arterial pressure increased before death. Repiration ceased when arterial blood pressure was about 35/8 mm Hg.

The 4 μmole/kg/min dose-rate of WR-6026 produced the same pattern of actions; however, the 2 dogs given this dose survived the 120 minute experimental period. Alterations in ECG patterns were prominent. Marked increases in P-R and Q-T intervals have been noted.

B. Minimum Effective Dose-rate of WR-6026 -- A dose-rate of 0.5 μmoles/kg/min has been noted in two dogs to produce only minor cardiopulmonary changes. Slight rises in systolic blood pressure and LV dP/dt have been noted during the drug infusion period. Respiratory rate and minute volume have also been modestly raised during this period.

Three pilot experiments employing 1.0 μmole/kg/min have demonstrated much more definite effects, some similar and others dissimilar. Left ventricular

dP/dt is elevated (5-12%) early in the infusion period (+5 min) and then falls to values slightly below baseline by the end of the infusion. Pulmonary artery pressure and pulmonary vascular resistance are modestly elevated during the infusions. The P-R and Q-T intervals are modestly increased by the 1.0 μmole/kg/min dose.

A dose-rate of 2.5 μmole/kg/min of WR-6026 produced effects intermediate to the other doses tested.

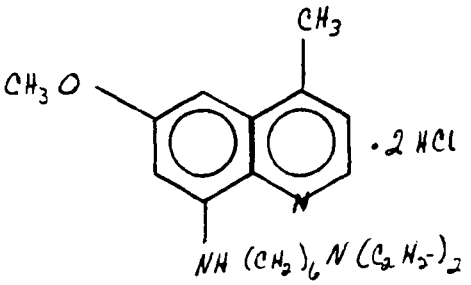
C. Previous Studies with Primaquine Diphosphate (hereafter referred to as primaquine) -- Primaquine, when infused i.v. at dose-rates of 0.5, 1.0, and 1.5 μmole/kg/min for 20 minutes in anesthetized dogs, produced changes in several pulmonary and cardiovascular variables. These changes occurred at a 4-fold lower dose-rate than those employed in the previous studies of mefloquine, quinine, and WR-184,806. The major effects of primaquine at dose-rates of 1.0 to 1.5 μmoles/kg/min were: 1) increases (30-50%) in pulmonary artery pressure and vascular resistance, 2) an approximately 30% prolongation of P-R interval and P wave and QRS complex duration which waned after cessation of infusion, 3) a transient depression of airway compliance, and 4) a modest production of methemoglobin (see Caldwell, R.W. and Nash, C.B. Interim Report No. 6, University of Tennessee, to WRAIR, 10 November 1980).

In this previous study, preliminary range-finding experiments demonstrated that a 2 μmole/kg/min dose-rate produced severe ventricular arrhythmias, including ventricular flutter, and caused death in 1 of the 2 dogs tested. One experiment is summarized in TRACINGS 2A,B,C&D. We conclude that high doses of primaquine have significant effects upon the pulmonary vasculature and cardiac electrical conduction.

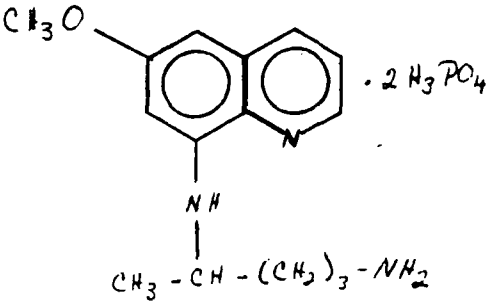
D. Present Studies with Primaquine -- We performed experiments during the winter of 1983 to determine if our previous range of primaquine dose-rates were appropriate. A 0.5 μmole/kg/min dose-rate of primaquine, again, proved to be the lowest which would consistantly produce some noticeable cardiopulmonary effect. The dose-cardiopulmonary response relationships for primaquine were considerably steeper than observed for the antimalarials we had studied previously (Caldwell and Nash, 1980).

In experiments to determine the maximum tolerated dose, we noted in 2 dogs that a dose-rate of 1.75 μmole/kg/min caused severe cardiopulmonary changes but did not result in death. Therefore, we tested primaquine at dose rates of 0.5, 1.0 and 1.75 μmoles/kg/min for 20 minutes in anesthetized dogs as a reference compound to compare the above stipulated doses of WR-6026.

Formulae for WR-6026•2HCl and Primaquine Diphosphate:



WR-6026·2HCl



Primaquine · 2 H_3PO_4

OUTLINE OF STUDIES

We used the following protocol and experimental scheme: Approximately 60 minutes were required following induction of anesthesia to perform the necessary surgery, cannulation procedures, and to establish calibrations. This was followed by a stabilization period of 20 to 30 minutes to insure that all recordings were steady, and this, in turn, was followed by a control period of 30 minutes during which data was recorded at 10-minute intervals. The drug infusion was then begun and continued for 20 minutes. There was a post-infusion period of 100 minutes for observation of recovery.

I. OBSERVATIONS -- 30-minute control period (-30,-20,-10, and 0 minutes)

A. Cardiovascular Measures

1. arterial blood pressure -- continuous
2. left ventricular pressure -- continuous
   a. dP/dt -- continuous
   b. left ventricular end diastolic pressure -- continuous
3. electrocardiogram -- at 10-minute intervals: all six limb leads are recorded at 25 mm/sec and strips at 100 mm/sec for analysis
4. heart rate -- continuous: by cardiotachometer
5. pulmonary vascular --
   a. pulmonary artery pressure -- continuous
   b. pulmonary wedge pressure -- at 10-minute intervals
   c. cardiac output -- at 10-minute intervals
   d. pulmonary vascular resistance -- calculated at 10-minute intervals

B. Pulmonary Ventilatory Measures

1. Airways differential pressures
   a. air flow -- signal integrated by preprogrammed computer
   b. transpulmonary pressure (bronchial vs esophageal) -- signals utilized by preprogrammed computer
2. Airways integrated measure -- tidal volume, continuous
3. Airways computer measures
   a. compliance -- continuous = $\Delta V/\Delta P$
   b. resistance -- continuous = $\Delta P/\Delta F$
4. Respiratory rate -- continuous

C. Hematological Measures - (-30 and 0 minutes only)

1. Blood P_{CO_2}-- arterial and venous
2. Blood P_{O_2}-- arterial and venous
3. Blood pH -- arterial and venous
4. Hematocrit -- central venous

II. DRUG INFUSION FOR 20 MINUTES -- Observations as described in I: A, B, and C. (Drug infusion time = 0 - +20 minutes)

A. Measures A and B from I., plotted at +10, and +20 minutes -- expanded record (25 and 100 mm/sec)
B. Measure C from I., plotted at +20 minutes

III. OBSERVATION PERIOD -- 100 minutes post-drug

A. Measures A and B from I., plotted at 10 minute intervals beginning at +30 minutes (beginning of drug = 0 time) -- expanded records
B. Measure C from I. taken at +40, +60, +80, +100, and +120 minutes

Experimental Groups

Group/Drug	Dose-Rate	Number of Dogs
1) WR-6026•2HCl	1.0 µmol/kg/min=.42 mg/kg/min	6
2) WR-6026•2HCl	2.5 µmol/kg/min=1.0 mg/kg/min	6
3) WR-6026•2HCl	4.0 µmol/kg/min=1.67 mg/kg/min	6
4) vehicle (control)	80 ml phosphate buffer (pH 7.4)	6
5) Primaquine•2H_3PO_4	0.5 µmol/kg/min=.27 mg/kg/min	6
6) Primaquine•2H_3PO_4	1.0 µmol/kg/min=.45 mg/kg/min	6
7) Primaquine•2H_3PO_4	1.75 µmol/kg/min=.80 mg/kg/min	6

METHODS

I. Drug Preparation and Delivery

WR-6026•2HCL (MW=416.44) (BN# BK01845) 6-Methoxy-8-(6-diethylamino hexylamino) lepidine dihydrochloride, supplied by WRAIR, was dissolved in phosphate buffer*, (pH 7.4) prepared fresh daily for each experiment. The WR-6026•2HCl

*Stock solutions A and B of:
A=27.8 g monobasic sodium phosphate in 1000 ml double distilled H_2O and
B=53.65 Na_2HPO_4•7H_2O in 1000 ml of double distilled H_2O; 19.0 ml A and 81.0 ml B were mixed and brought to a total volume of 200 ml

is readily soluble in the desired concentrations. Primaquine•$2H_3PO_4$ (MW=455.35, AldrichChem Co., lot #2429BE, 99+% by certificate of purity, -see Appendix H) was purchased. The concentration of the solution was adjusted to the weight of each dog such that a fixed intravenous volume infusion rate of 4.0 ml/min contained the appropriate amount of drug, as the salt, in moles. The total volume infused over 20 minutes was, thus, 80 ml.

II. Animals

Mongrel dogs of either sex, weighing between 8.0 and 15.0 kg were supplied by the University of Tennessee Vivarium for these studies. The dogs were physically examined for disease symptoms and only animals that appeared healthy and had a normal ECG were accepted for the study. One ml of blood was taken and checked for presence of microfilaria using the Knott's test (Knott, 1939) before the experiment. Dogs were anesthetized with pentobarbital Na, 30 mg/kg intravenously, and maintained with intravenous injections of 1.0 mg/kg as necessary to maintain a stable anesthesia. The absence of corneal and plantar reflexes, response to pain, and a respiratory rate of 16-20 breaths/min were used in "titrating" the dog to the desired level of anesthesia.

III. Cardiovascular Measurements

N. B. 1. See Appendix of protocol for WR-228,258, Dec. 1981, for details of instrument calibration procedures.

2. See Cardiovascular Measurements Section of protocol for WR-228,258, Dec. 1981, for details; procedures were the same except the blood sampling procedures that follow:

IV. Blood Sampling Procedures

A period of about 30 minutes was allowed following surgical and recording instrument preparation for the dog to assume stable cardiorespiratory function.

At this point, the first arterial and venous blood samples (6 ml each) were withdrawn following evacuation of the void volume in the arterial and venous cannulas. The glass syringes used were lubricated with mineral oil and rinsed prior with heparinized saline (500 units/ml). Syringes containing blood were immediately capped with tight-fitting rubber nipples and put in ice until analysis. The first samples drawn were designated as -30 minutes. At time 0, the beginning of the 20 minute i.v. infusion of pH 7.4 phosphate buffer or drug solution at 4 ml/min, another set of blood samples were taken. Additional sets of blood samples were taken at +20, +40, +60, +80, +100, and +120 minutes. Withdrawal of blood was performed by a person other than the operator of the blood gas analyzer. All samples were immediately capped, placed in ice and analyzed by using the Corning, Model 165/2,Blood Gas Analyzer in accordance with the manufacturer's instructions, within the intervening 20 minute period or as rapidly as possible. In addition, she ran three microhematocits on all blood samples. We established the sensitivity for the Corning Blood Gas Analyzer, Model 165/2 and our precision for analyzing pO_2, pCO_2 and pH using the test format established by Corning (See Appendix G). We used Curtin Mathison Gas Trak control standard samples for testing the normal, alkalotic and acidotic states for the above indicated variables. Each 6 ml sample was analyzed in triplicate. We identified and eliminated outliers using the technique of Dixon, 1953. A critical alpha

value of 0.10 represents a reasonable, critical value for exclusion of outliers in this study. We entered mean values for blood chemistry variables in the accompanying tables. Raw data entries for the blood chemistry variables remain on file at the investigators' laboratory and in the Archives at the Division of Experimental Therapeutics, WRAIR.

V. Pulmonary Ventilatory Measurements

For the measurement of pulmonary function, while breathing room air unassisted, an endotracheal tube with a side arm was connected directly to a mesh screen Fleish pneumotachograph and the pressure difference across the screen measured by a differential pressure transducer (Validyne transducer, Model MP45-24). This signal, when calibrated against a known air flow, corresponds to tidal airflow rate and, in turn, when integrated, yields tidal volume. An esophageal tube (Porter ID6•5) was inserted into the esophagus for the assessment of intrapleural pressure. The pressure difference between the airway and esophagus, or transpulmonary pressure, was measured by a second differential pressure transducer (Validyne transducer Model MP45-14). Dynamic airway resistance and dynamic airway compliance were derived using a Buxco Electronics Pulmonary Mechanics Computer, Model 6, and were recorded along with tidal volume on a Grass, Model 7b, polygraph.

N.B. 1. See the Pulmonary Ventilitory Measurements Section of the Appendix of protocol of WR 228,258, Dec. 1981, for details of theory for structural program for the derivation of dynamic resistance and dynamic compliance and the appropriate calibration procedures for each variable using the Buxco computer.

VI. Data Presentation

Samples of analog tracings for cardiovascular and respiratory indices illustrate changes that take place due to primaquine and WR-6026, with respect to baseline and vehicle control. All measurements called for in this study are presented in tabular form using percent change of baseline where baseline equals 100 percent (unless otherwise indicated). Summary graphs have been constructed to show percentage change from baseline (or control) which we established as 100 percent. Variability for each measurement is entered as ± 1 S.E.M. for the mean percent of baseline (unless otherwise indicated). We established baseline at 100% for the variable levels at 0 time. A graphic representation of each variable defines the comparative responses to all dose levels of a test substance with respect to vehicle control (PO_4 buffer). A composite of the related single variables, one for the cardiovascular system and one for the respiratory system for each test substance, facilitates an understanding of response mechanisms for these organ systems to the intravenous infusion of the test substance.

RESULTS

Pulmonary Function

A summary of all baseline (time zero) data as absolute values appears in Table 1 (appendix B). The raw experimental data for each dog is given in tables of Appendix F.

Baseline values for respiratory rate in the seven experimental groups ranged from 5.2±1.0 to 8.6±1.8 cycles/min (Table 1). Phosphate buffer vehicle infusion appeared to cause an increase in respiratory rate, perhaps due to an

effect of volume or to constituents of the buffer. Infusion of 1.0 μmoles/kg/min of WR-6026 increased the respiratory rate prominently over the first 10 minutes of infusion, but the rate was about that of the control group from +20 min on (Fig 1a). Both the higher dose-rates of WR-6026 increased respiratory rate as much as 180% above control valves at +20 mins.; this tachypnea was maintained. Primaquine at the two lower dose-rates did not alter respiratory rate (Fig 1b). The 1.75 μmoles/kg/min dose-rate produced a transient elevation of rate of about 100% during the infusion. This tachypnea waned quickly with the cessation of infusion.

Baseline tidal volume values for these groups at time zero ranged from 249±13 ml/breath to 370±71 ml/breath and, in general, correlated with weights of the dogs. Tidal volume dropped by about 20% during infusion of PO_4 buffer. The 1.0 μmoles/kg/min dose-rate of WR-6026 had no effect on tidal volume but the middle dose-rate infusion was associated with about a 15% depression of this variable (Fig 2A). Tidal volume tended to be depressed by the high dose-rate but responses were quite variable. Primaquine at the high dose-rate also depressed tidal volume; but the other dose-rates did not produce any significant change (Fig 2B).

Minute volume, which is the product of the average tidal volume and respiratory rate, was increased by WR-6026. At zero time the baseline values for the experimental groups ranged from 1.54±0.25 to 2.68±0.46 ℓ/min (Table 1). All dose-rates of WR-6026 produced a similar peak rise in minute volume at +10 min. (Fig 3A). Minute volume for the upper dose-rate groups remained elevated throughout the rest of the observation period; minute volume for the low dose group returned towards control values by the end of the infusion. Primaquine had no significant effect upon minute volume (Fig 3B).

Airways compliance remained fairly stable in the control group given phosphate buffer (Fig 4A&B); baseline values for the experimental groups ranged from 18.8±3.1 to 35.3±8.0 cu (Table 1). WR-6026 had no apparent effect upon airways compliance at any dose-rate (Fig 4A). Primaquine appeared to increase airways compliance at the lower dose-rate (from +30→+50 mins.), but depressed airways compliance at the middle dose. The high dose-rate of primaquine had no effect (Fig 4B).

Airways resistance for the seven experimental groups at baseline time point (time 0) ranged from 5.6±2.8 to 12.5±3.7 ru (Table 1); phosphate buffer infusion (control) tended to depress resistance, but values were quite variable. The two higher dose-rates of WR-6026 depressed airways resistance over the entire experimental period; the low dose-rate of WR-6026 had no effect (Fig 5A). Primaquine had no obvious action on airways resistance (Fig 5B).

Blood oxygen tension in arterial samples was not affected by either WR-6026 or primaquine (Figs 6A&B). Venous blood oxygen was also not affected by these drugs (Figs 7A&B).

Blood carbon dioxide tension tended to drop in all groups during the infusion period (Figs 8A&B and 9A&B). There were, however, no apparent drug-related effects.

Blood pH values remained essentially the same throughout the experimental period for each of the groups (Figs 10A&B and 11A&B). There was some variability in values among the groups. Venous blood hematocrit was not affected by any of the drug treatments (Figs 12A&B).

Cardiovascular Function

Baseline heart rate ranged from 138±10 to 165±23 beats/min (Table 1). Phosphate buffer infusion tended to depress heart rate. WR-6026 had no affect on heart rate except, perhaps, causing a small rise after +10 min of the high dose-rate (Fig 13A). Primaquine given at both the high and low dose-rates had no action upon heart rate; the middle dose, however, appeared to elevate heart rate by about 20% (Fig.13B).

Diastolic blood pressure at zero time ranged from 106±9 to 119±11 mmHg (Table 1). This variable dropped by about 10 - 15% in the control group over the course of the experimental period (Fig. 14A and 14B). The middle and high dose infusion of WR-6026 transiently depressed diastolic blood pressure by about 20 - 25%. The low dose group demonstrated a stable diastolic pressure over time (Fig 14A). Primaquine did not affect diastolic blood pressure at the dose-rates tested (Fig 14B).

Systolic blood pressure values at time zero range from 162±12 to 186±17 mmHg (Table 1). Neither WR-6026 nor primaquine altered systolic blood pressure at the dose-rates tested (Figs 15A&B).

Cardiac contractile force, as indicated by left ventricular (LV) dP/dt (Figs 16A&B), waned slightly in the controls during the infusion of phosphate buffer but stabilized after +30 min. Baseline (Time 0) values for LV dP/dt ranged from 1710±450 to 3020±380 mmHg/sec in the seven groups (Table 1). LV dP/dt was severely depressed by the upper two dose-rates of WR-6026 (Fig 16A). Contractility was maximally depressed at the end of the infusion to 50% and 42% of baseline. Recovery from the effects of these dose-rates was slow and only partial to 60% of baseline. The low dose-rate of WR-6026 did not

depress cardiac contractility. In contrast, primaquine at all doses tested did not acutely affect LV dP/dt (Fig 16B). LV dP/dt, however, gradually fell from +80 to +120 min in the primaquine-treated groups.

Cardiac Output values at zero time ranged from 1.54±0.17 to 1.95±0.21 ℓ/min (Table 1). Cardiac output in the control group was maintained until about +90 min when it began to fall (Figs 17A&B). The high dose-rate of WR-6026 appeared to depress cardiac output by about 20% at the end of the infusion; the middle dose-rate depressed cardiac output markedly, also, during infusion. In general, cardiac output was depressed during the middle of the infusion period in the 2 elevated doses (Fig 17A). The low dose-rate of WR-6026 was without effect. Primaquine had no effect on cardiac output (Fig 17B).

Pulmonary artery pressure (PAP) was prominently elevated during the infusion of the high dose-rate of WR-6026 (Fig 18A); PAP, in this group, returned to baseline levels by about +50 mins. The low and middle dose also elevated PAP by +20 mins but the magnitude of the response was considerably less. Primaquine modestly elevated PAP at the middle and high dose-rate; the low dose had no action on PAP (Fig 18B). Baseline PAP values ranged from 9.4±1.5 to 16.3±3.0 mmHg (Table 1). Phosphate buffer infusion appeared to depressed PAP.

Pulmonary Vascular Resistance (PVR) changes were, in general, similar to those of pulmonary artery pressure. Baseline values ranged from 5.5±0.8 to 9.2±1.6 mmHg/l/min (Table 1). The low dose-rate of WR-6026 did not significantly alter PVR (Fig 19A). The higher doses, however, caused prominent elevations of PVR during the infusion; PVR in these groups rapidly

returned to baseline values after the WR-6026 infusion, but tended to remain slightly above values in the control group. Primaquine at the upper two dose-rates produced only a modest elevation of PVR (Fig 19B). The low dose group for primaquine displayed a response similar to that observed for control vehicle infusion, a slow gradual fall.

Pulmonary wedge pressure (PWP) values at time zero ranged from 1.4±0.8 to 3.5±1.2 mmHg among the groups (Table 1). Phosphate buffer infusion did not alter PWP. The high and middle dose-rates of WR-6026 caused marked rises in PWP; PWP returned toward baseline values over 40 min after the infusion (Fig 20A). The low dose of WR-6026 produced only a modest rise in PAP. Primaquine infusion produced rises in PWP, but the magnitude of the effect was considerably less than that observed with WR-6026 (Fig 20B). The rise in PWP due to the high dose infusion was the most prominent (3.5 mmHg).

Electrocardiographic Effects

WR-6026, 4 µmole/kg/min, did not cause any abnormal beats in any animals; there was no change in rhythm or QRS configuration; and no significant alteration in P-wave, T-wave, or electrical axis of the ventricle (Table 2). There was a 75% increase in QRS width, a 42% increase in P-R interval, and a 43% increase in Q-T interval by the end of drug administration. These effects waned following the infusion. Even with the maximum change in duration of the P-R, Q-T intervals, & QRS, these values are within the normal range of values for dogs (Crawley and Swenson, 1966).

Primaquine, 1.75 µmole/kg/min caused similar but somewhat lesser changes in P-R interval (increased 30%), in QRS width (increased 33%), and Q-T

interval (increased 10%) at + 20 min. These changes also diminished soon after the infusion. Primaquine did not alter the QRS configuration, P-wave, T-wave, or electrical axis of the ventricle. One dog in the high dose group developed a sustained run of ventricular flutter and tachycardia during the drug infusion which reverted after 25 minutes. Pilot experiments indicated that a 2.0 μmole/kg/min dose of primaquine produces this arrhythmia. The vehicle infusion caused no consistent or significant changes, with the possible exception of a 14% decrease in heart rate.

The overall effects of WR-6026 on the EKG were rather modest at the high dose. The increase in P-R interval indicates some interference with A-V transmission and the prolongation of the QRS width and Q-T interval suggests a depression of ventricular conduction and repolarization. However, none of these changes resulted in development of ectopic beats or a change in rhythm. Primaquine, on the other hand, did cause ventricular flutter and tachycardia in one animal, even though conduction changes were smaller than those from WR-6026.

Representative tracings of EKG leads I, II and III for each of the experimental groups is given in Figure 21.

SUMMARY OF CARDIOVASCULAR COMPOSITE DATA

WR-6026 (Composite Figures 1 and 2)

Heart rate changes with the three dose levels did not follow a dose-response pattern and were of minor importance. Systolic blood pressure gradually declined by some 10 - 15% and a similar decline was seen in the vehicle control group. Again, a strict dose-response pattern was not seen.

However, diastolic blood pressure did decrease more than the control group during drug infusion at the high dose, and possibly at the middle dose also. No fall in diastolic blood pressure was seen at the low dose; on the contrary, it tended to remain slightly above the controls. Cardiac outputs drifted downwards some 20 to 30% over the experimental period, including the control group. The low dose group was quite similar to the control group, while the upper two dose groups were below control most of the experimental period, with the middle group being the lowest. The one measurement that was clearly affected the most was contractile force. Control dP/dt decreased about 15-20% over 2 hours and the lower dose group closely paralleled the control. The middle and high doses caused a maximum fall in contractile force during the infusion of about 50%, and these two groups were only different from each other for a short period near the end of the first hour. Even after two hours, the dP/dt was still down to 60% of control, indicating a long lasting weakening of contractile force.

In the pulmonary vascular bed, arterial pressure was above control values at all three dose levels for the first hour, and this was especially prominent with the high dose. The middle and high doses also caused a sharp rise in wedge pressure, lasting at least an hour. Pulmonary vascular resistance was significantly elevated by the two higher doses. Resistance quickly recovered to a plateau near the zero time value but was still above the control group. The decrease in contractile force, causing an overfilling of the left atrium, is reflected in the sudden increase in wedge pressure. A considerable vasoconstriction of the pulmonary bed is indicated by the prominent increase in resistance to the two higher doses.

Primaquine (Composite Figures 3 and 4)

The middle dose of primaquine produced a modest increase of some 15% in heart rate, bordering on significance. However, the high and low doses were not different from, and closely parallel to, the control group. No important changes in either systolic blood pressure or diastolic blood pressure occurred during the infusion, although during the last 20 minutes or so of the experiment both pressures were somewhat above controls at the 1 μM low dose. Contractile force declined steadily at all dose levels but was only prominently depressed during the last 30 minutes. Since the greatest effect was caused by the lowest dose, no dose-effect relationship was seen. Cardiac output progressively declined with all groups, including the controls. Thus, no significant homodynamic effects were seen.

Pulmonary artery pressure fell about 30% during infusion of the vehicle. The low dose of primaquine produced similar changes, but the middle and high dose resulted in an elevation of pulmonary artery pressure during the infusion with the high dose causing the greatest effect. The middle dose response recovered in about 40 to 50 minutes while the pressor response to the high dose was still evident at the conclusion of the experiment. Wedge pressure was elevated by all three doses. Responses to the low and middle doses waned within 60 minutes. The high dose produced the greatest rise but pressure had quickly recovered by 40 minutes and fell below control during the last hour.

Primaquine exhibited dose-effect responses in the pulmonary vascular bed, in contrast to the systemic vascular system. Pulmonary resistance was unaffected by the low dose; modestly increased by the middle dose; and

significantly increased by the high dose. The changes in pulmonary resistance seemed to be persistent, and above control at the end of the experiment.

SUMMARY OF RESPIRATORY COMPOSITE DATA

WR-6026 (Composite Figure 5)

A prompt and marked increase in respiratory rate was produced by all dose-rates of WR-6026 tested; the minute volume was elevated with the profile of changes for these dose-rates against time being quite similar to the pattern for respiratory rate. The upper two dose-rates produced elevations in these variables which endured for the entire experimental period. Tidal volume was only transiently diminished during drug infusion.

Airway resistance dropped during the infusion of the upper two dose-rates; the same groups which exhibited the marked rises in respiration rate and tidal volume. As was noted for these latter variables, the depression in resistance was maintained for the entire experimental period. Airways compliance was not affected by this drug.

Primaquine (Composite Figure 6)

Only the high dose-rate of primaquine elevated respiratory rate and only during the drug infusion. Because tidal volume fell during this period, minute volume was not affected.

Airways resistance was not altered by primaquine. This drug, however, may have varied actions on airways compliance, elevating compliance at a low dose and depressing it at a higher dose.

DISCUSSION

It is clear from our data that both WR-6026 and primaquine produce steep dose-response curves for cardiopulmonary actions; both possess a maximum tolerated dose/minimum effective toxic dose ratio of about 4. On a molar basis, two times more of WR-6026 is required to produce cardiopulmonary toxic responses than primaquine. The most dangerous effect of WR-6026 is progressive depression of cardiac contractility to the point of ineffective cardiac pumping. In contrast, the potentially lethal action of primaquine is upon cardiac rhythm.

Pulmonary: WR-6026 possesses a greater ability to raise respiratory rate than does primaquine. The mechanism for the maintained tachypnea produced by the upper doses of WR-6026 is unknown. However, no other aminoquinoline studied so far has such potential [see studies of Caldwell and Nash on WR-228,258 (1982) and WR-184, 806 (1978)].

The tachypnea produced by both drugs was, in general, associated only with a modest fall in tidal volume. Thus minute volume, the product of tidal volume and rate, was prominently elevated by administration of WR-6026. This increase in pulmonary air movement was not associated with a drug-related fall in blood carbon dioxide tension.

Neither drug had remarkable actions on airways compliance. Primaquine may have exerted a biphasic action, which depended on dose. The lower dose-rate slightly raised compliance while the middle dose depressed it. The mechanism for such actions is not apparent; primaquine did not exert prominent effects upon the pulmonary vasculature which might be involved in altering airways compliance.

Airways resistance was decreased throughout the observation period by the middle and upper dose-rate of WR-6026. This effect might be considered beneficial. Such an action is unusual for the quinolines with which we have experience. Mefloquine causes a prominent and dose-related elevation of airways resistance (Caldwell and Nash, 1976). WR-228,258 did not produce changes in airway resistance (Caldwell and Nash, 1982). Whatever the mechanism for reduced airways resistance, it does not appear to involve β-adrenergic receptors as changes in cardiovascular functions expected in response to β-adrenergic agonists and sympathetic nerve stimulation were not observed.

Blood gas tension was not affected remarkably by either drug. The only possible exception was an apparent rise in venous P_{O_2} at the end of the high dose-rate infusion of primaquine. The change was not striking in graphic data of averages, but was apparent with inspection of data from individual experiments. These observations suggest primaquine may depress peripheral O_2 utilization.

Cardiovascular: None of the heart rate changes in this study were impressive. WR-6026 produced a small decrease at the end of the perfusion, as did the vehicle. With primaquine, there were only minor fluctuations with the high dose, although the 1.0 μmole/kg/min dose caused a small increase of borderline significance. There is little to indicate any important effects of WR-6026 on the automaticity of the heart, either directly or indirectly via the autonomic nervous system.

Over the period of the experiment systolic and diastolic blood pressures tended to drift downward with the vehicle group. The initial vasodepression

by WR-6026 was transient as blood pressure recovered rather promptly after the end of the infusion and neither WR-6026 nor primaquine produced any lasting effect on blood pressure. It seems that neither drug has any prominent or persistent vasodilating action.

WR-6026 produced a clear-cut depression of contractile force which began with the initiation of the middle and high dose infusions, and reached maximum depression at the end of the infusion. This indicates a direct cardiac depressant action by WR-6026 which is persistent since there was only a partial recovery of contractility during the 20 minutes after the infusion, and a stable lower level was maintained from about 40 minutes to 120 minutes. Primaquine was distinctly different since it did not cause any changes in dP/dt during the infusion, although a slow, steady decrease in contractile force had just reached a significant difference at the end of the experimental period. Primaquine, thus, may have a degree of cardiac depression of slow onset; however, WR-6026 definitely causes cardiac weakening with an immediate onset.

It is well documented that the anesthetized dog under barbiturates will experience a gradual fall in cardiac output over a period of a few hours (Nash, 1956). In this study the vehicle group confirmed previous findings in this regard. Primaquine infusions resulted in decreases in cardiac output which closely paralleled the vehicle group; indicating that primaquine had no significant effect on cardiac output. WR-6026 tended to reduce cardiac output at the two higher doses. It is probable that the reductions in cardiac output are related to the depression of myocardial contractile force and changes in total vascular resistance produced by WR-6026.

In the pulmonary vascular bed, WR-6026 raised the pulmonary artery pressure in a dose-related manner during the drug infusion. The pressor effect declined rather promptly with cessation of infusion and was not different from the vehicle group from about +60 minutes to the end of the experiment. Primaquine had a similar effect and the PAP elevation at the high dose was definitely longer lasting. Both drugs appear capable of causing pulmonary vasoconstriction in a dose-related manner. They differ in that WR-6026 has a strong acute effect of short duration while primaquine has an initial effect of lesser intensity but is more prolonged and even tends to increase with time as indicated by the data on pulmonary vascular resistance.

Pulmonary wedge pressure is an indirect indicator of left atrial pressure. Primaquine infusion initially raised PWP as the drug was increased. WR-6026 in the two higher doses resulted in a considerable increase in PWP which recovered within 40 to 50 minutes. These data indicate that blood was backing up in the left atria due to the depression of contractile force, and WR-6026 was more active in these doses than primaquine.

The electrocardiograms indicated that WR-6026, and to a lesser degree primaquine, produced a slowing in A-V transmission and a slowing in ventricular conduction. However, it is doubtful if the changes seen at these doses are of great significance in themselves, since the values were still within the range of normal measurements (Crawley and Swenson, 1966). On the other hand, it does indicate that both drugs have the potential for interfering with transmission and conduction. The outstanding finding was the development of serious ventricular arrhythmias by primaquine. One animal in the primaquine group had an episode of ventricular flutter/tachycardia lasting

for 25 minutes. In two other dogs in the range-finding experiments, primaquine caused fatal and near fatal ventricular arrhythmias. In contrast, no such events were seen with WR-6026.

Conclusions: WR-6026 may produce prominent depression of cardiac contractility, elevate respiratory rate and depress airways resistance. Primaquine has far less prominent actions on cardiovascular, hemodynamic, and pulmonary variables. Both agents slow A-V nodal and ventricular conduction velocity; primaquine, however, may produce dangerous ventricular arrhythmias.

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COMPARISON OF CARDIOVASCULAR AND PULMONARY EFFECTS

OF

WR-6026-2HCl and PRIMAQUINE DIPHOSPHATE

March 2, 1984

These studies were conducted in accordance with current Good Laboratory Practice Regulations of the Food and Drug Administration, dated December 22, 1978, with subsequent ammendments.

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APPENDIX A
LEGEND OF TERMS USED

Abbreviation	Definition
TV-ml/breath	Tidal Volume-ml/breath
Resp-breaths/min	Respiration Rate-breaths/min
MV-1/min	Minute Volume-liters/min
C-cu	Respiratory Dynamic Compliance-compliance units
R-ru	Respiratory Dynamic Resistance-respiratory units
SBP-mmHg	Aortic Systolic Blood Pressure-mmHg
DBP-mmHg	Aortic Diastolic Blood Pressure-mmHg
ABP-mmHg	Aortic Blood Pressure
HR-beats/min	Heart Rate-beats/min
C.O.-1/min or CO	Cardiac Output-liters/min
dP/dt-mmHg/sec	Acceleration of pressure, a quantitative expression for defining contractility of the heart
PWP-mmHg	Pulmonary Wedge Pressure - an estimate of left atrial pressure
PAP-mmHg	Pulmonary Artery Pressure
PVR-mmHg/1/min	Pulmonary Vascular Resistance
A-Po_2-mmHg	Arterial Blood Oxygen Tension
A-Pco_2-mmHg	Arterial Blood Carbon Dioxide Tension
A-pH	Arterial Blood pH
V-Po_2-mmHg	Venous Blood Oxygen Tension
V-Pco_2-mmHg	Venous Blood Carbon Dioxide Tension
V-pH	Venous Blood pH
Hct-% cells	Hematocrit-% Red Blood Cells

Appendix B

Tables 1 and 2

Table 1
baseline values ± 1 S.E.M.

	PO_4-buffer	WR-6026 1.0 µmole/kg/min	WR-6026 2.0 µmole/kg/min	WR-6026 4.0 µmole/kg/min	Primaquine 0.5 µmole/kg/min	Primaquine 1.00 µmole/kg/min	Primaquine 1.75 µmole/kg/min
TV-ml/breath	333 ± 60	306 ± 34	356 ± 36	342 ± 52	269 ± 34	370 ± 71.4	249 ± 13
Resp-breaths/min	8.0 ± 2.8	6.2 ± 1.3	5.6 ± 0.9	8.6 ± 1.8	8.5 ± 2.2	5.2 ± 1.0	6.1 ± 0.8
MV-l/min	2.09 ± 0.[illegible]	1.79 ± 0.30	2.00 ± 0.41	2.68 ± 0.46	2.11 ± 0.59	1.70 ± 0.17	1.54 ± 0.25
C-cu	31.3 ± 8.0	35.3 ± 8.0	18.8 ± 3.1	24.0 ± 6.0	22.9 ± 7.5	21.5 ± 4.4	26.3 ± 5.1
R-ru	11.2 ± 7.6	9.0 ± 7.0	5.9 ± 1.0	12.5 ± 3.7	6.4 ± 3.3	11.2 ± 3.8	5.6 ± 2.8
SBP-mmHg	162 ± 12	171 ± 14	173 ± 11	178 ± 11	186 ± 17	183 ± 20	165 ± 8
DBP-mmHg	109 ± 8	106 ± 9	116 ± 3	110 ± 10	113 ± 10	119 ± 11	115 ± 6
HR-beats/min	165 ± 23	152 ± 13	159 ± 11	156 ± 15	160 ± 15	138 ± 10	155 ± 14
C.O.-l/min	1.54 ± 0.17	1.71 ± 0.18	162 ± 0.10	164 ± 0.07	1.75 ± 0.13	1.95 ± 0.21	1.58± 0.15
dP/dt-mmHg/sec	1710 ± 450	2560 ± 330	2400 ± 530	2580 ± 360	3020 ± 380	2330 ± 400	2470 ± 390
PWP-mmHg	2.4 ± 0.9	2.5 ± 0.8	3.5 ± 1.2	1.4 ± 0.8	2.2 ± 1.1	3.2 ± 1.2	1.7 ± 1.0
PAP-mmHg	13.8 ± 2.2	9.4 ± 1.5	12.5 ± 2.4	12.7 ± 2.2	14.5 ± 2.2	16.5 ± 3.0	10.2 ± 1.4
PVR-mmHg/l/min	9.2 ± 1.6	5.5 ± 0.8	7.9 ± 1.5	7.7 ± 1.3	8.4 ± 1.4	8.4 ± 1.3	6.6 ± 0.9
A-Po_2-mmHg	70.5 ± 6.3	66.3 ± 9.6	74.8 ± 7.2	72.0 ± 4.3	74.0 ± 4.6	68.8 ± 7.0	70.4 ± 6.9
A-Pco_2-mmHg	43.2 ± 3.2	47.1 ± 6.0	45.2 ± 3.3	40.2 ± 2.7	43.7 ± 2.7	46.6 ± 3.0	47.2 ± 3.5
A-pH	7.306 ± 0.034	7.251 ± 0.045	7.298 ± 0.020	7.296± 0.031	7.312 ± 0.020	7.250 ± 0.030	7.276 ±0.030
v-Po_2-mmHg	45.4 ± 2.2	41.2 ± 5.7	44.7 ± 2.3	38.9 ± 1.7	45.1 ± 2.5	40.8 ± 2.7	43.2 ± 3.8
v-Pco_2-mmHg	47.9 ± 3.8	53.6 ± 5.3	52.6 ± 2.8	48.4 ± 2.8	48.6 ± 2.6	54.9 ± 3.5	52.8 ± 3.3
v-pH-	7.284 ± 0.034	7.222 ± 0.039	7.259 ± 0.020	7.248 ± 0.034	7.268 ± 0.020	7.216 ± 0.030	7.261 ±0.030
Hct-% cells	36.2 ± 3.1	39.4 ± 2.6	41.1 ± 3.2	32.9 ± 2.5	39.0 ± 2.67	39.2 ± 3.34	39.1 ± 4.1

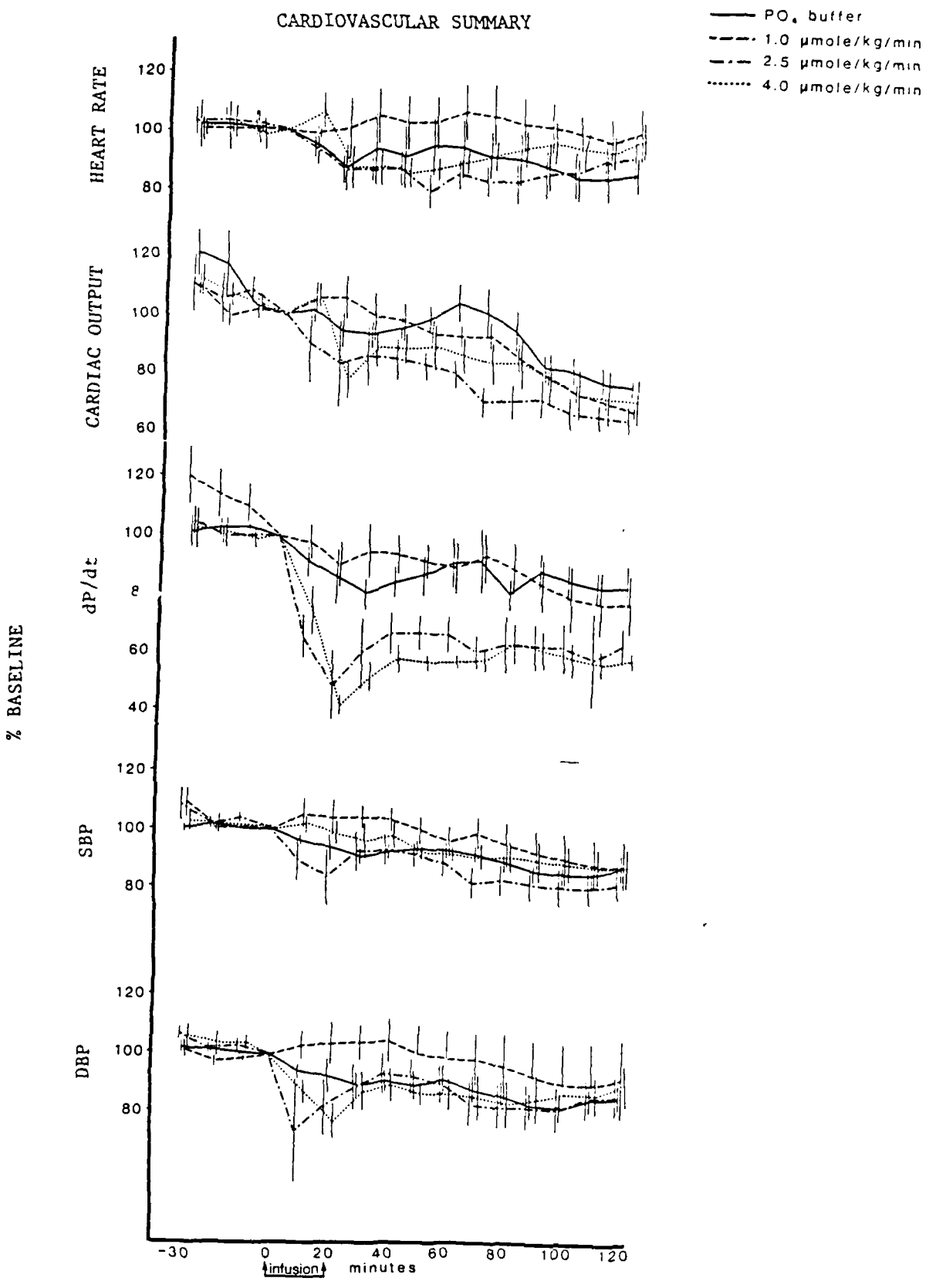
Appendix C

Composite Summaries

Note: All variation bars represent S.E.M.

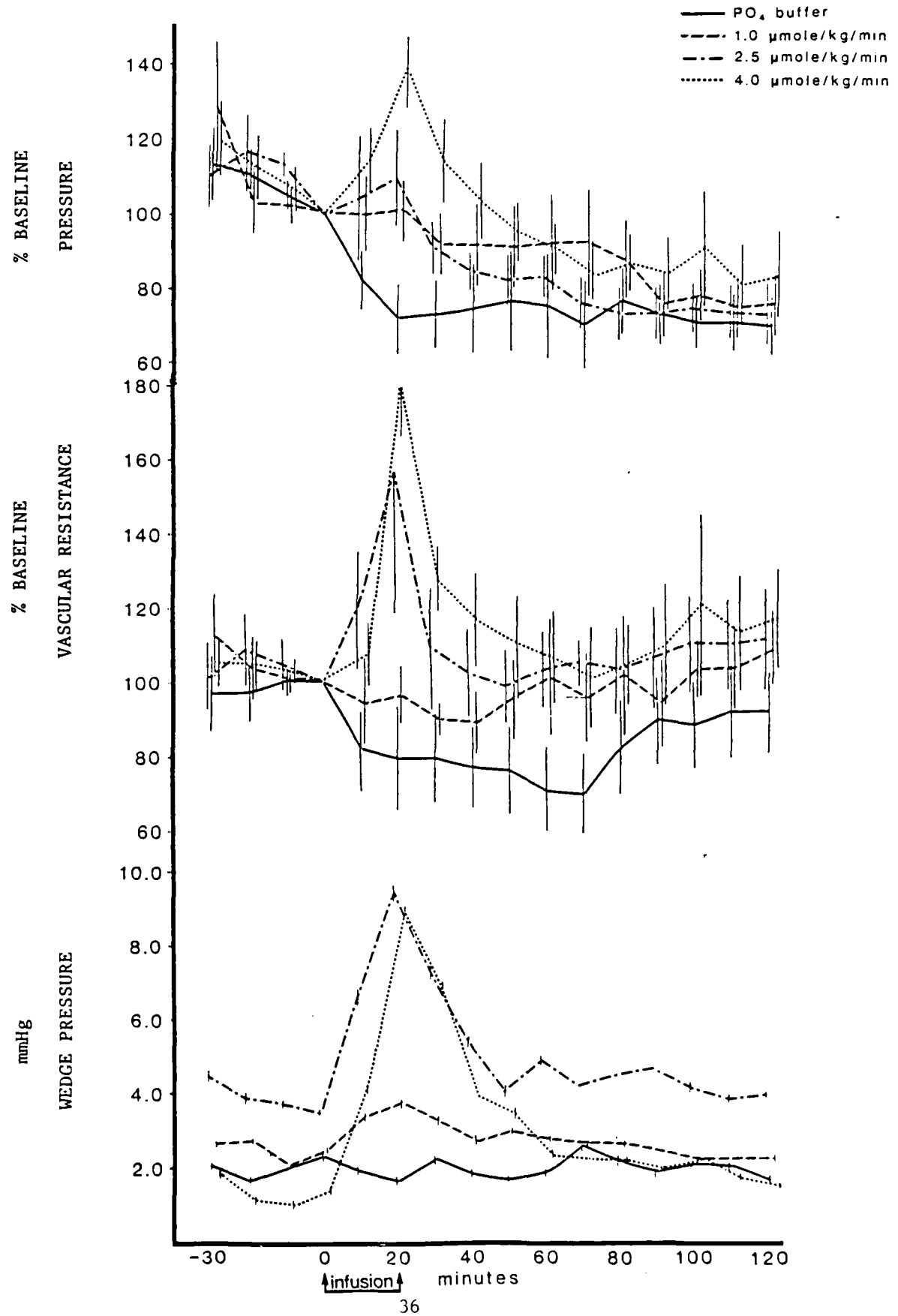
composite fig. 1

WR-6026



WR 6026 composite fig. 2

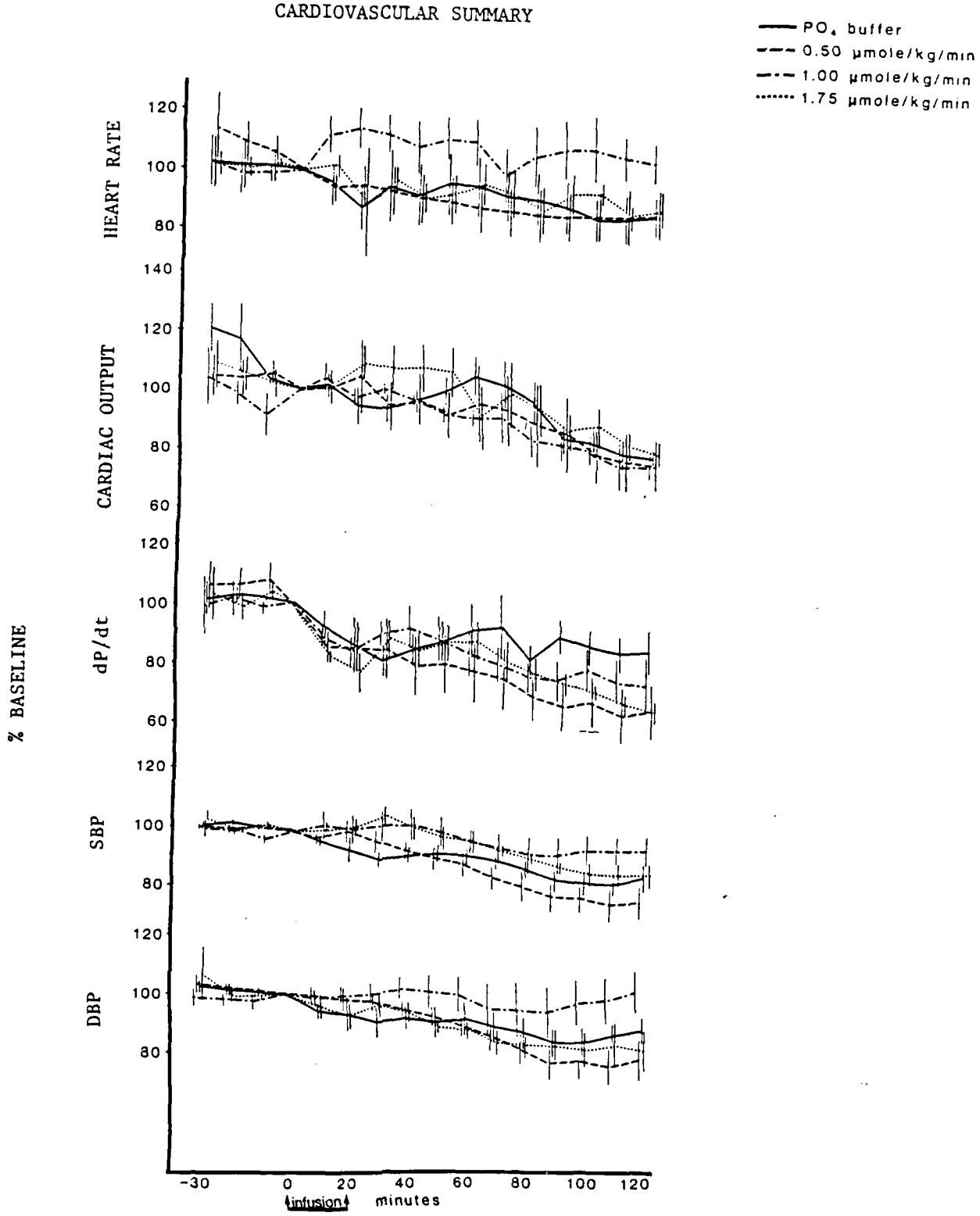
PULMONARY ARTERY SUMMARY



composite fig. 3

PRIMAQUINE

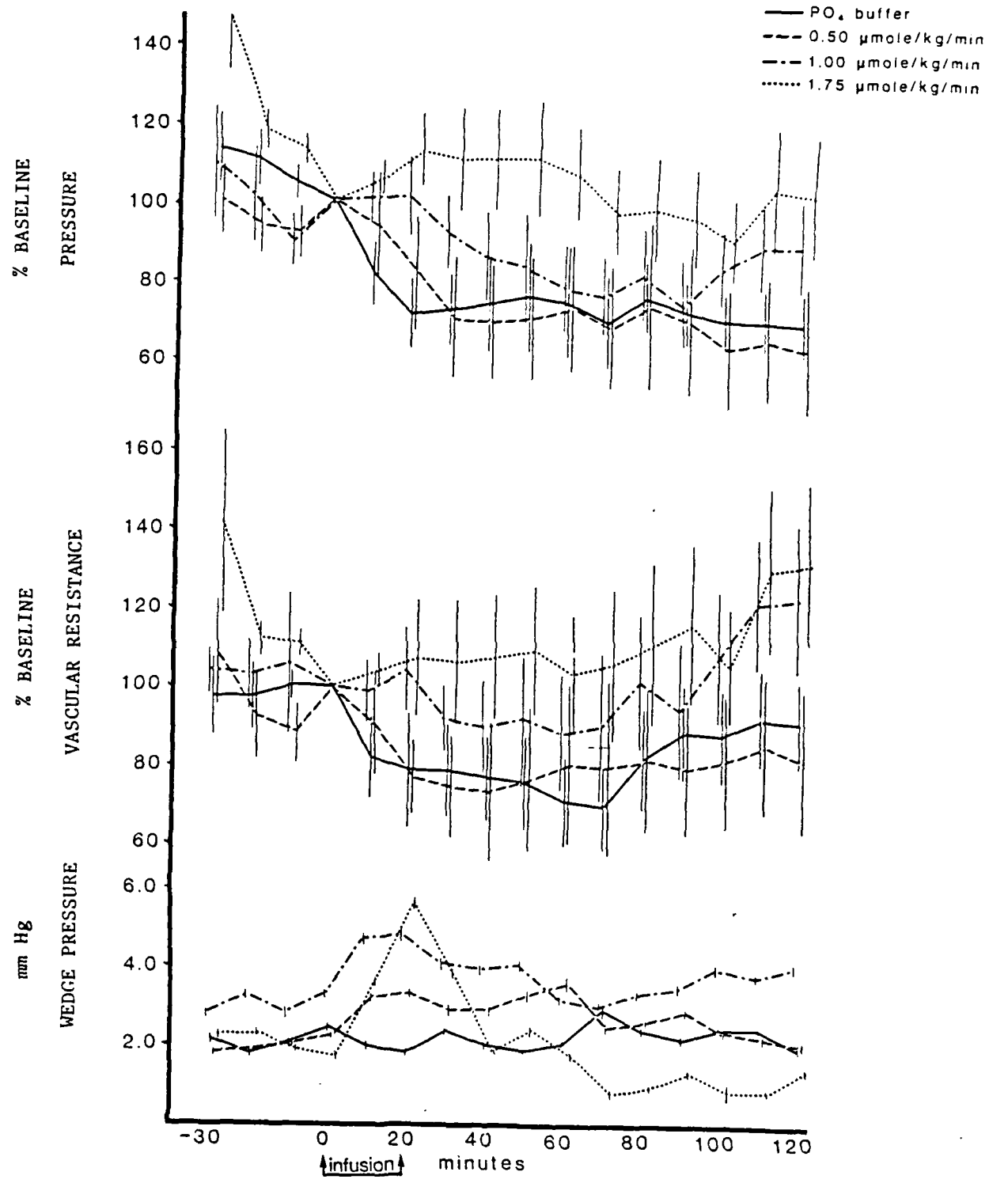
CARDIOVASCULAR SUMMARY



PRIMAQUINE

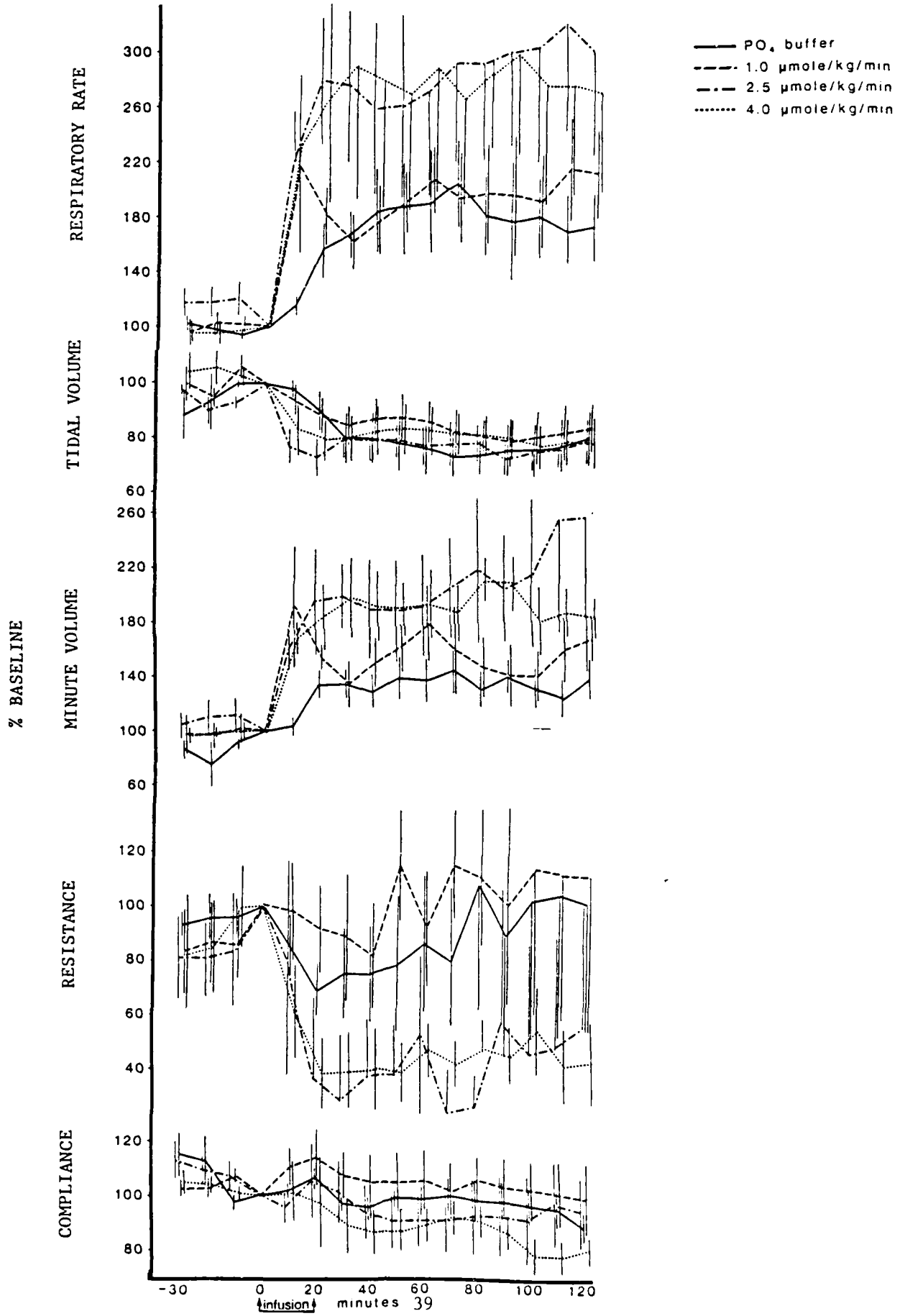
composite fig. 4

PULMONARY ARTERY SUMMARY



RESPIRATORY SUMMARY

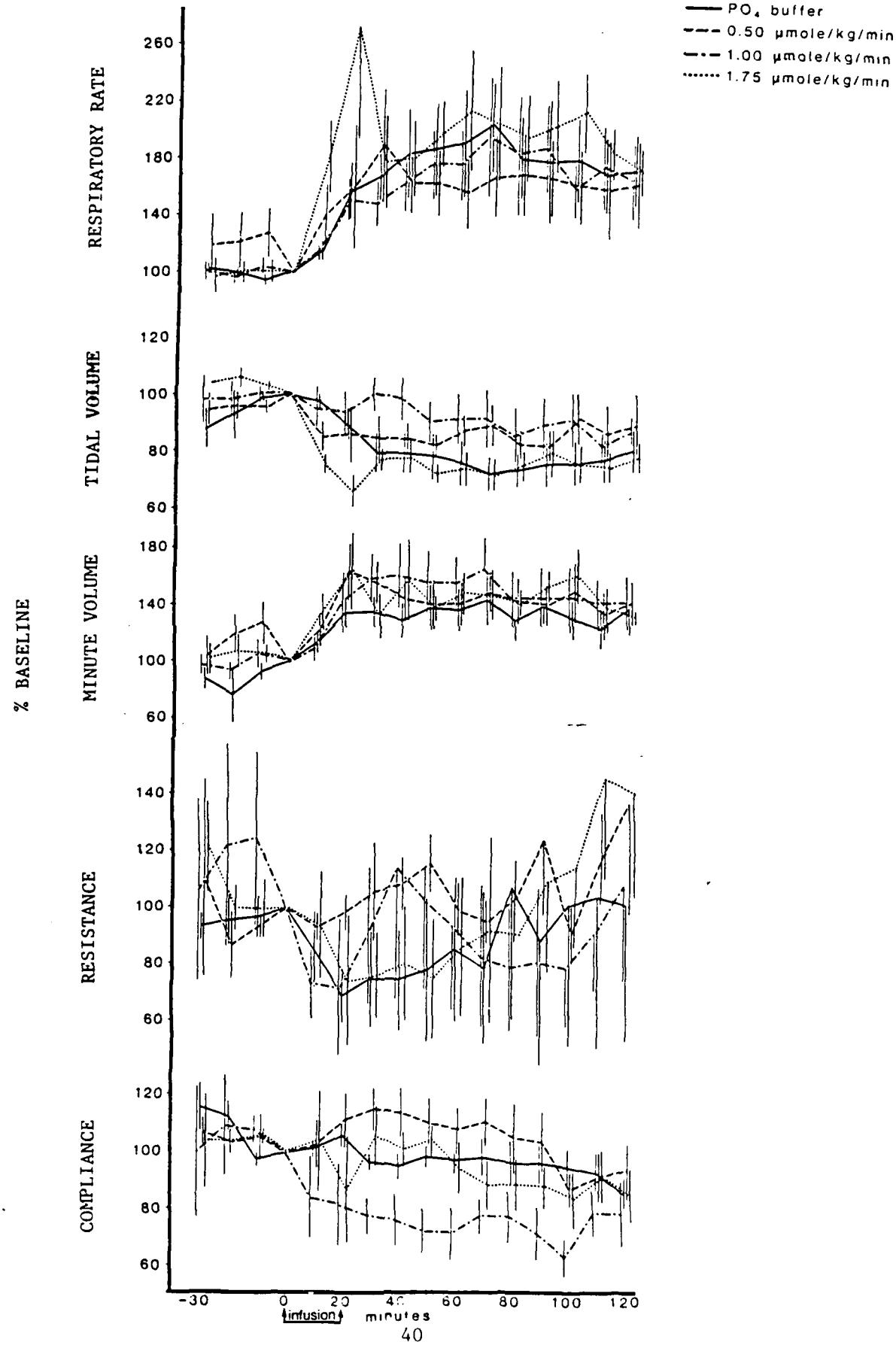
composite fig. 5



PRIMAQUINE

RESPIRATORY SUMMARY

composite fig. 6



APPENDIX D

Variable Plots

Note: All variation bars represent S.E.M.

figure 1A

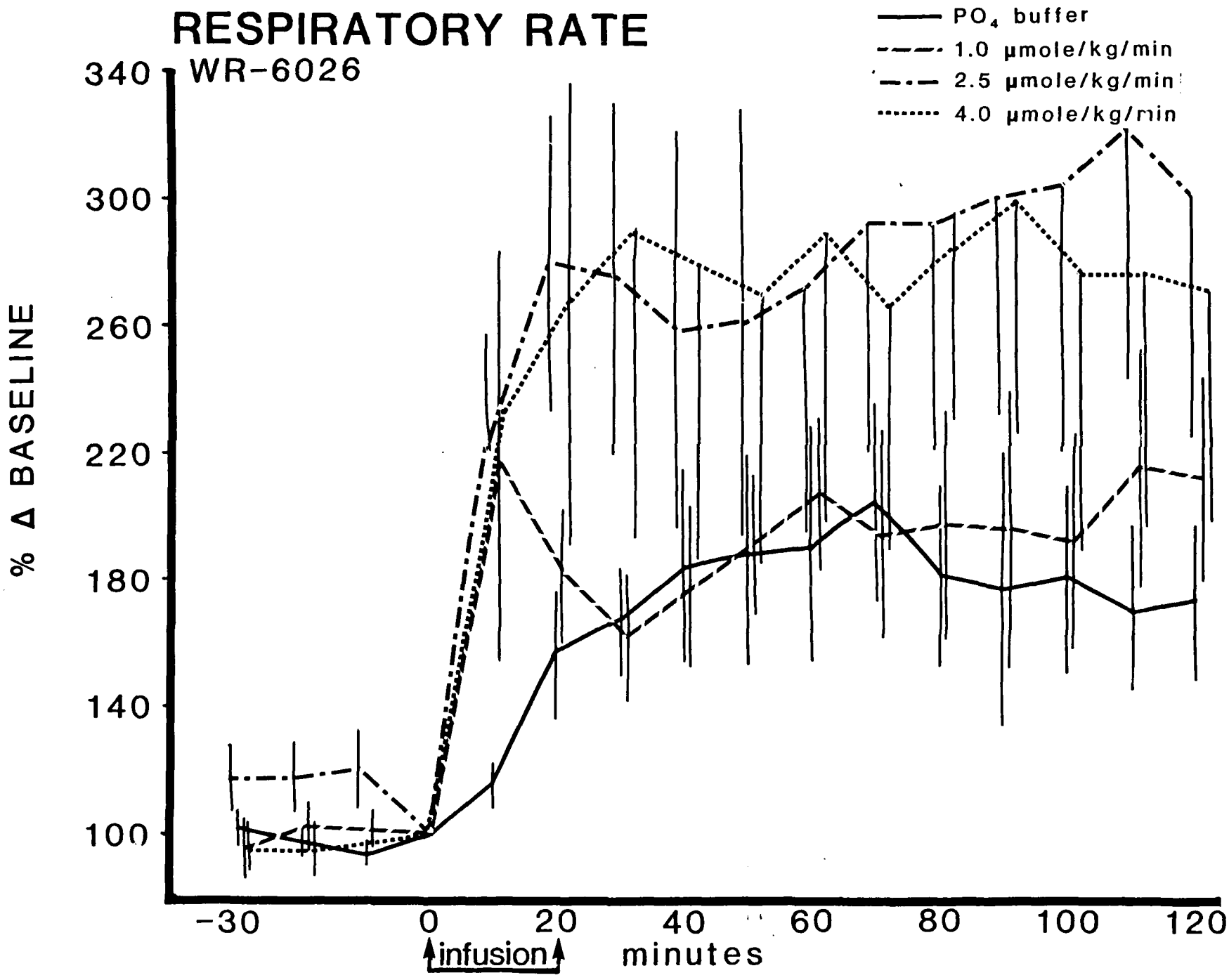

RESPIRATORY RATE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
340
300
260
220
180
140
100
-30
0
20
40
60
80
100
120
infusion
minutes

figure 1B

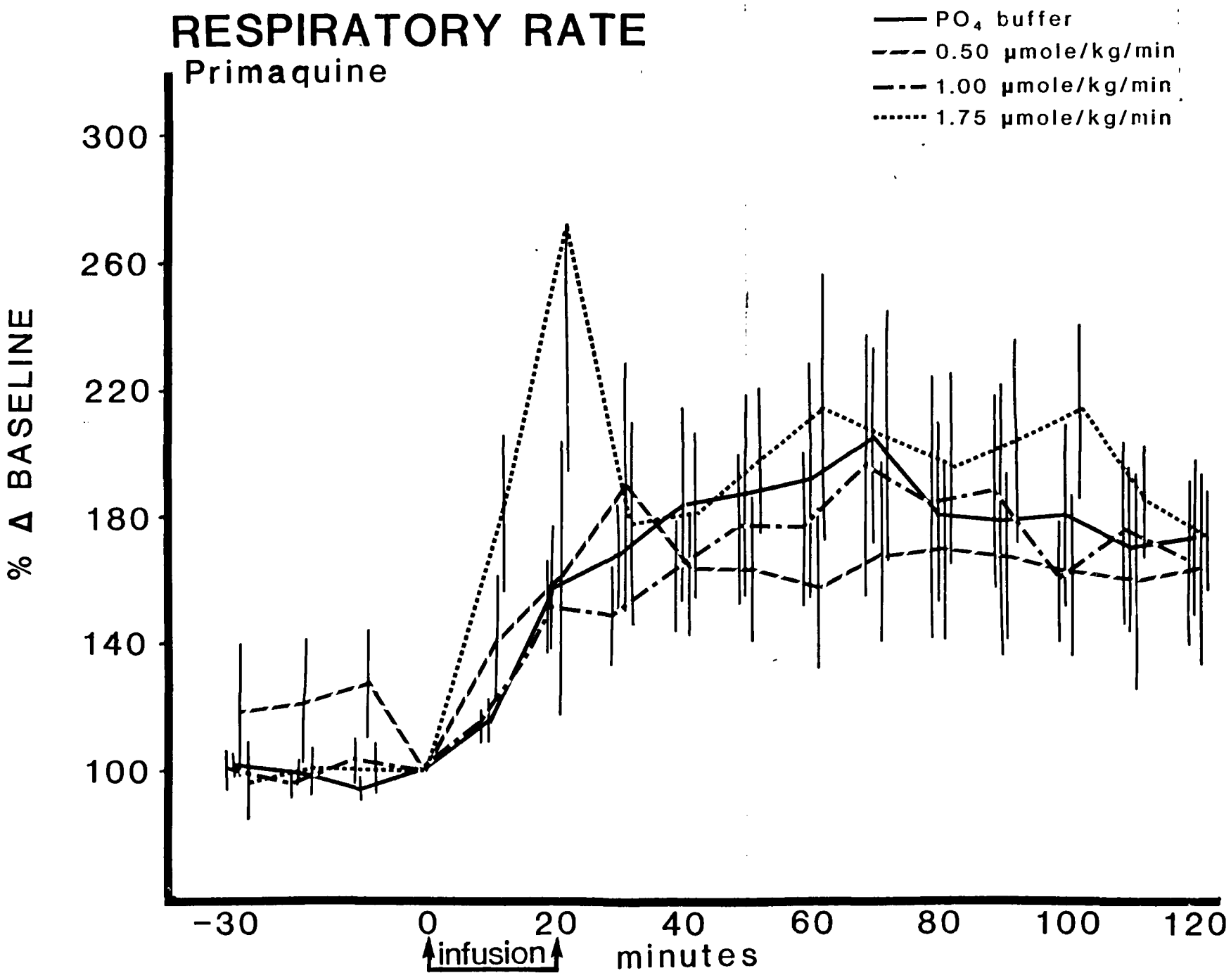

RESPIRATORY RATE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
300
260
220
180
140
100
-30
0
20
40
60
80
100
120
infusion
minutes

figure 2A

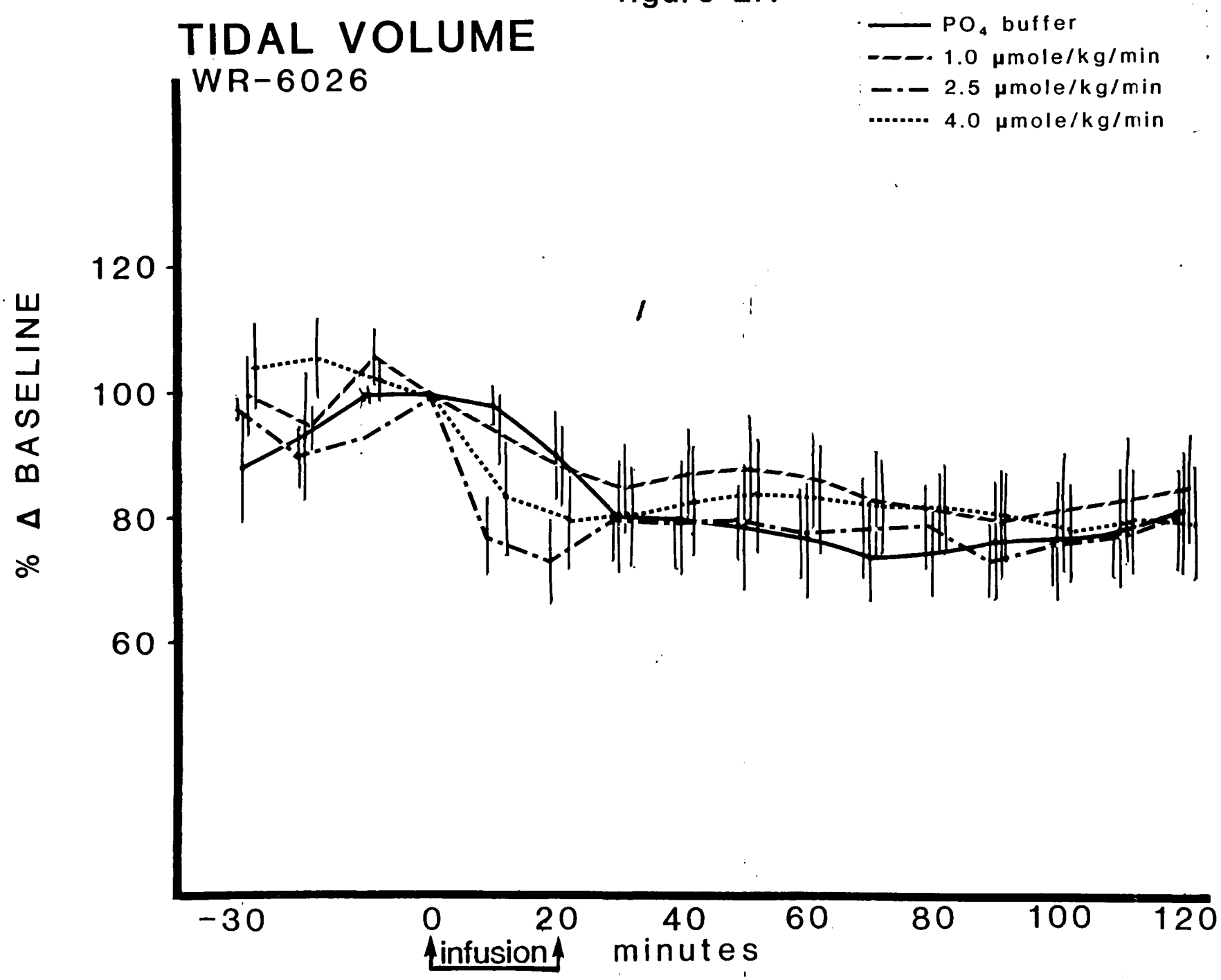

TIDAL VOLUME
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 2B

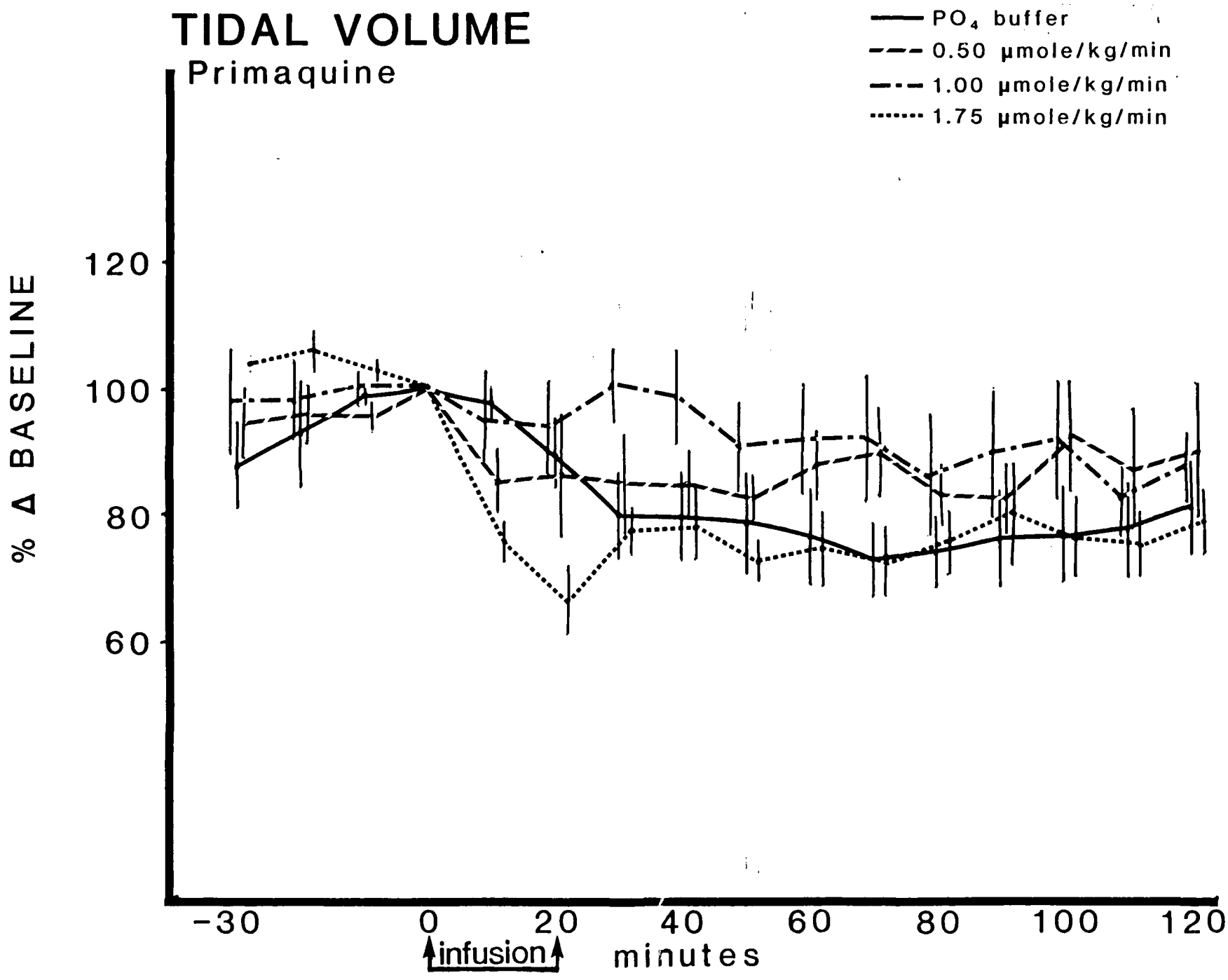

TIDAL VOLUME
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 3A

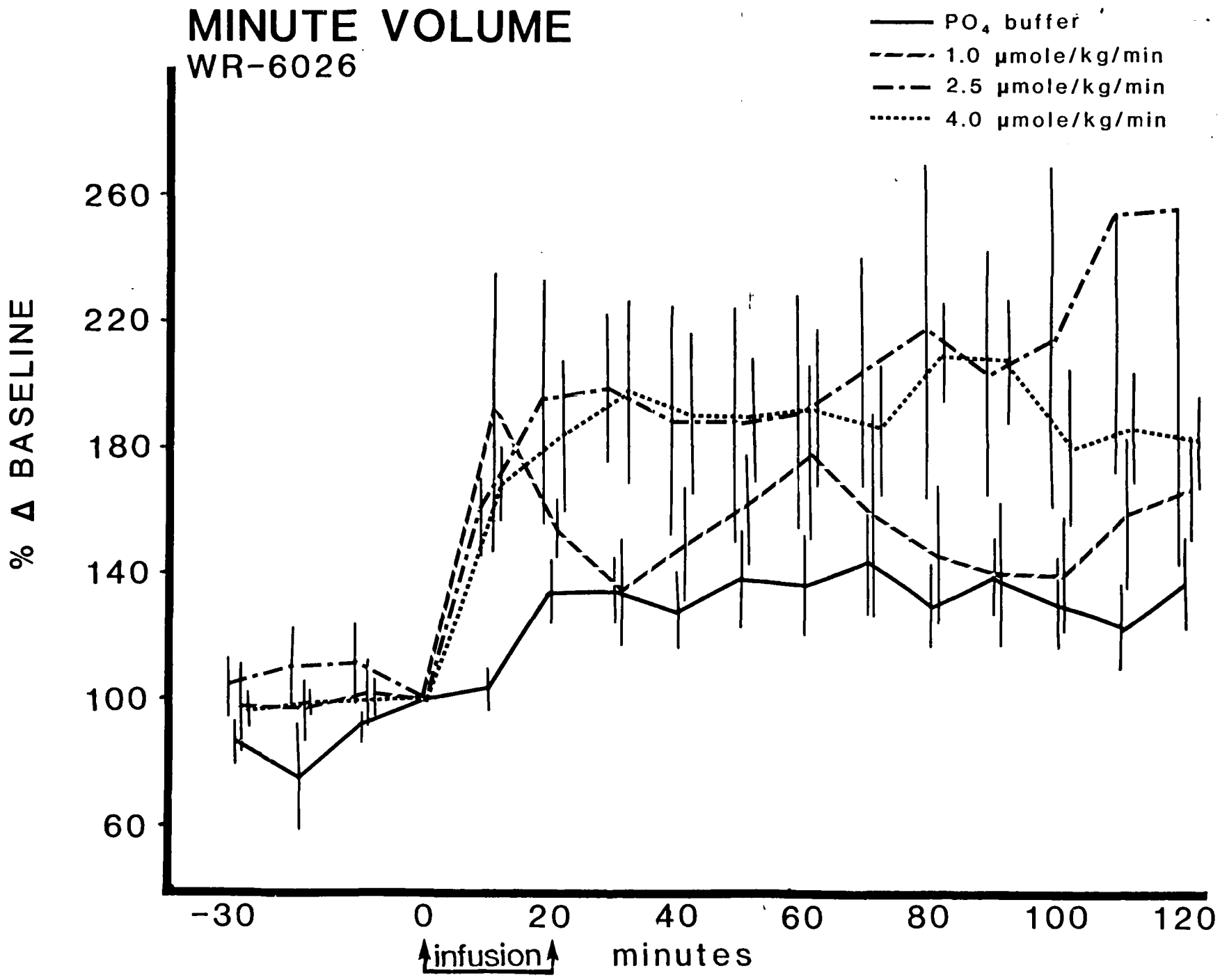

MINUTE VOLUME
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
260
220
180
140
100
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 3B

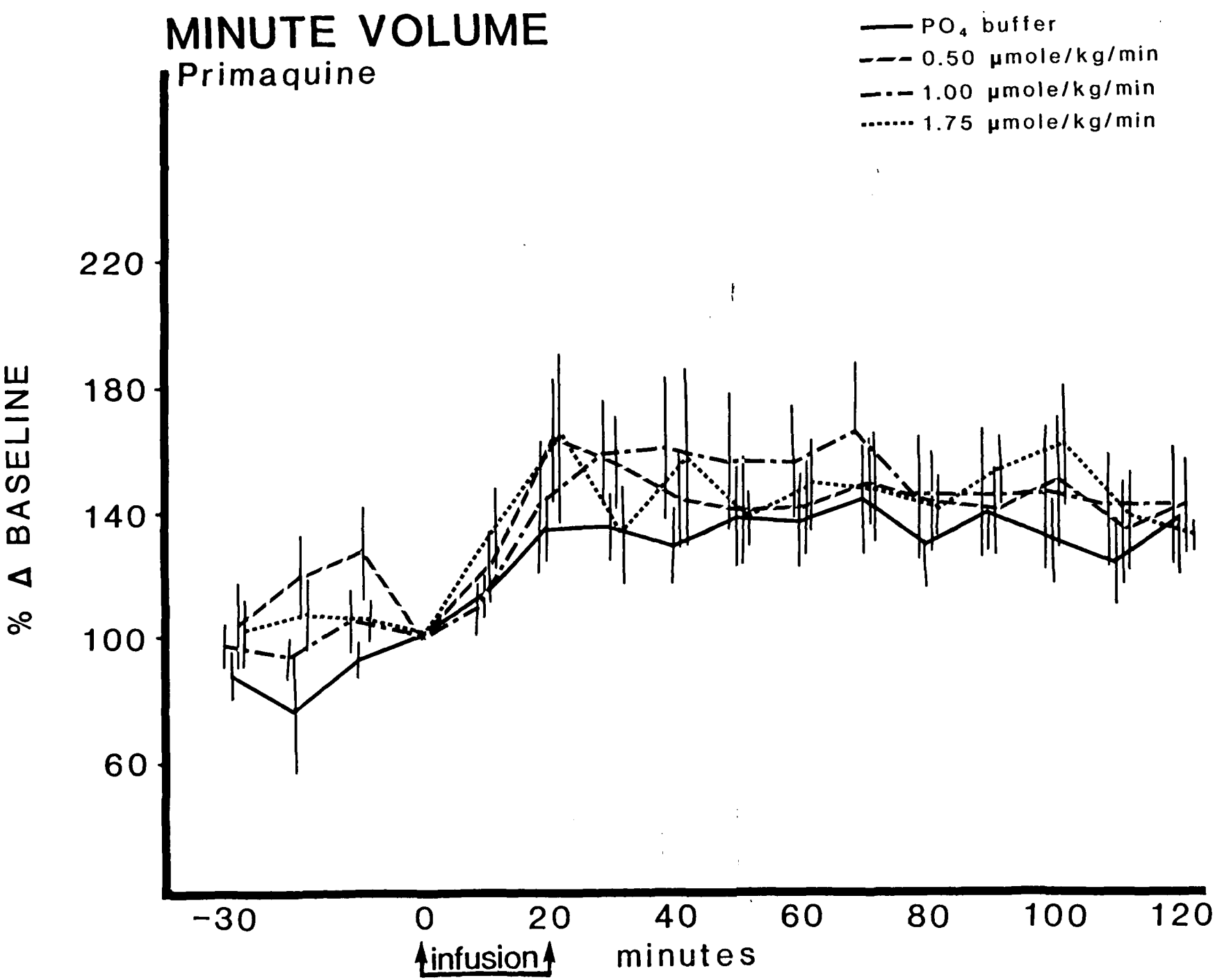

MINUTE VOLUME
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
220
180
140
100
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 4A

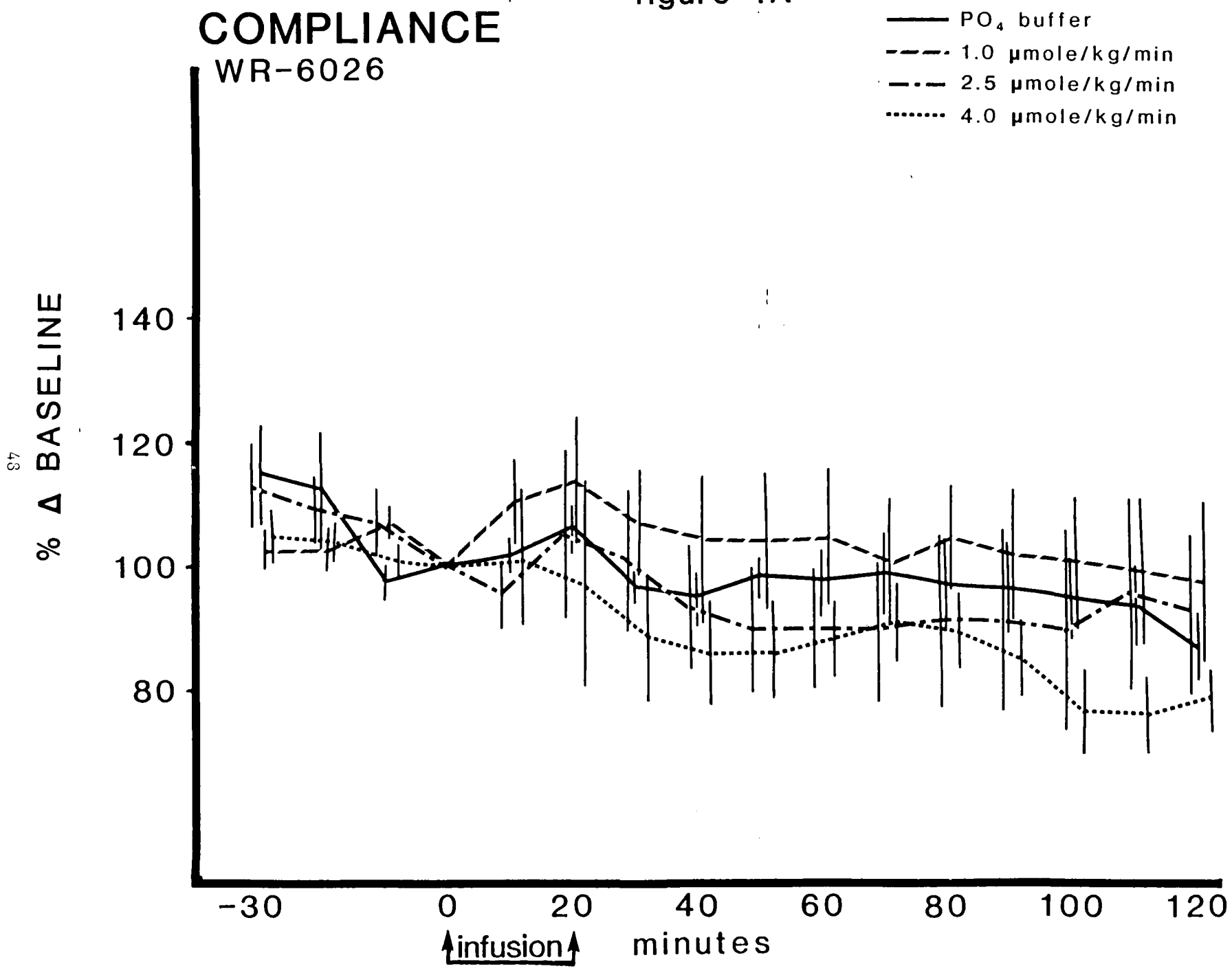

COMPLIANCE
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
140
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 4B

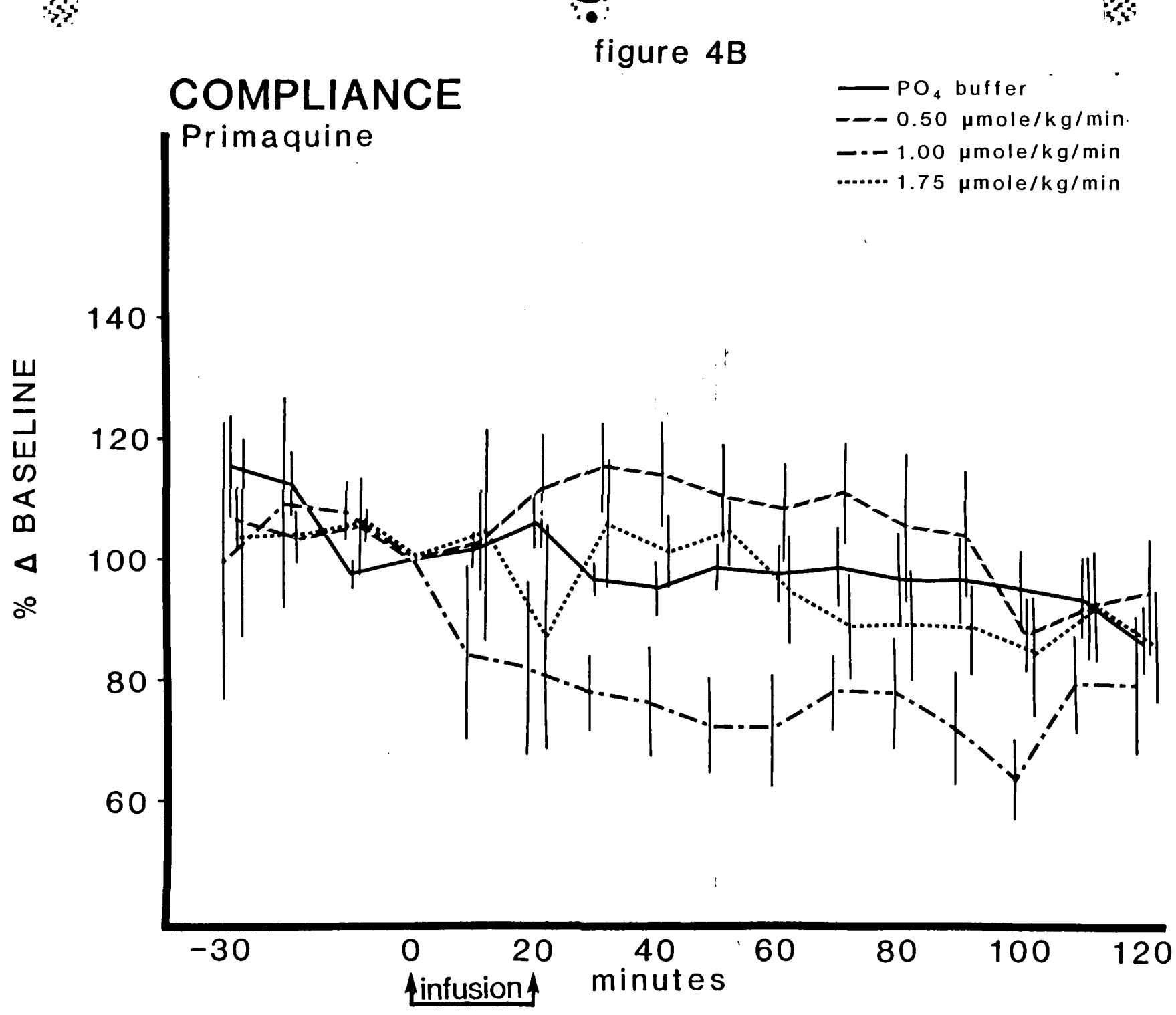

COMPLIANCE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 5A

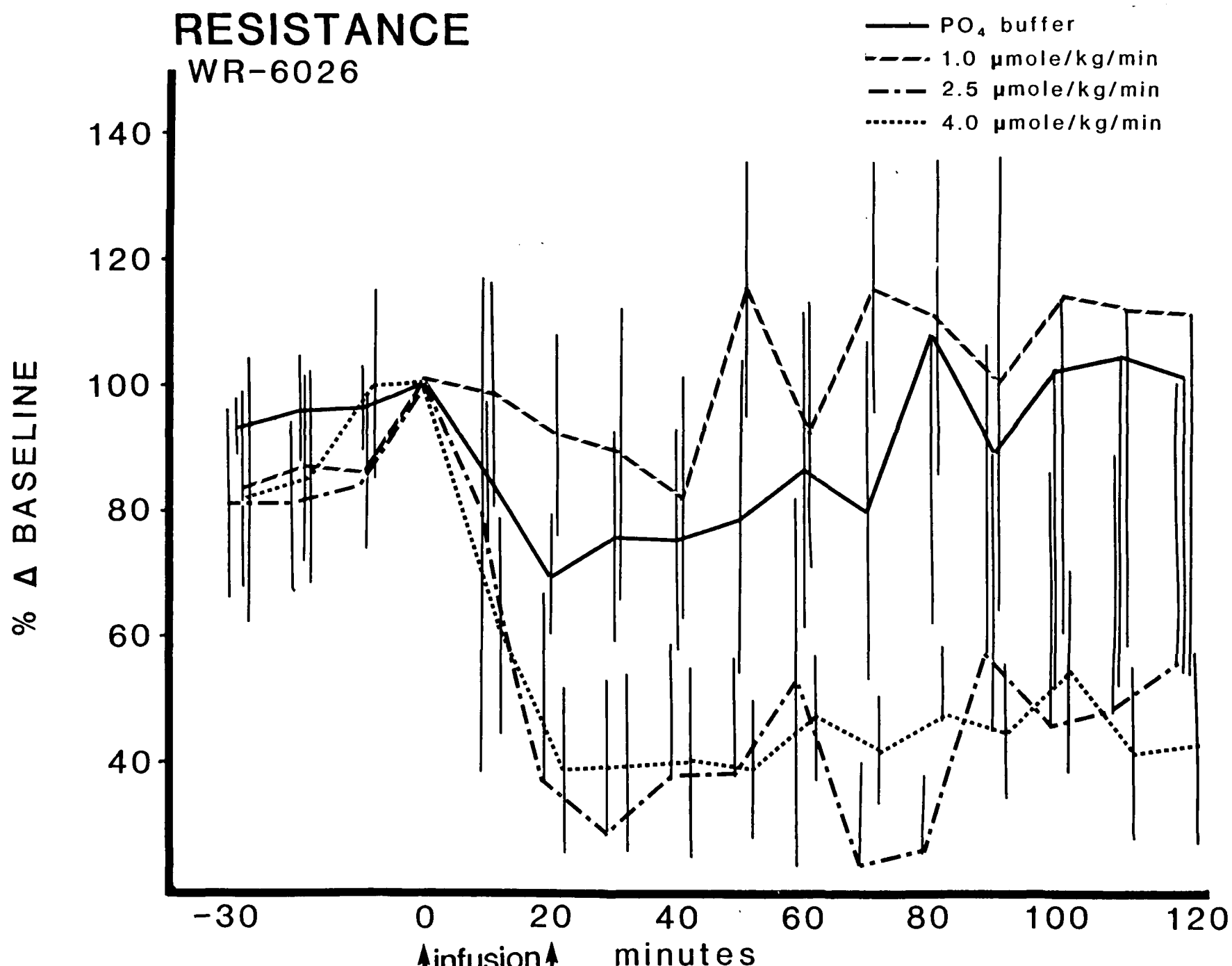

RESISTANCE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
140
120
100
80
60
40
-30
0
20
40
60
80
100
120
infusion
minutes

figure 5B

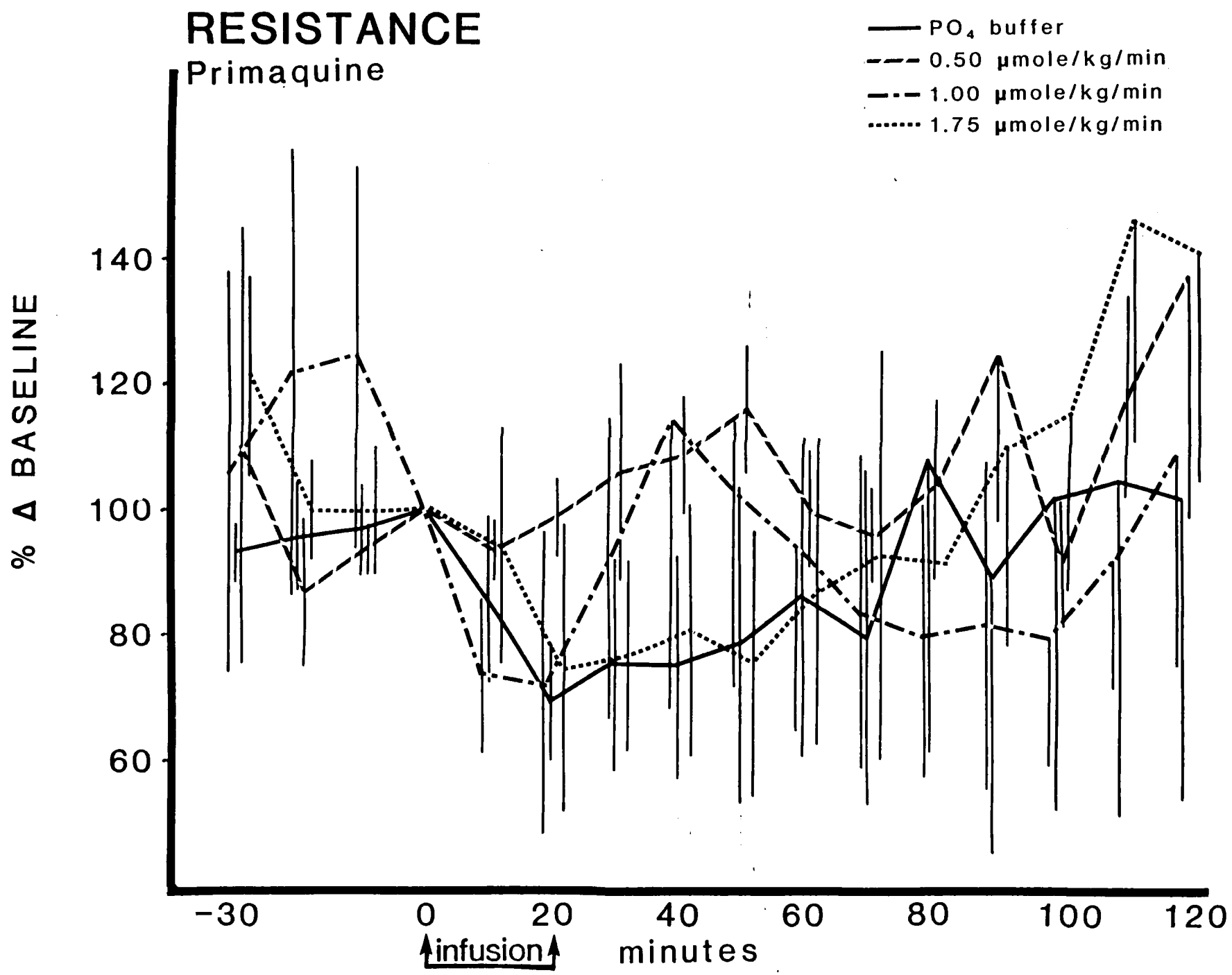

RESISTANCE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 6A

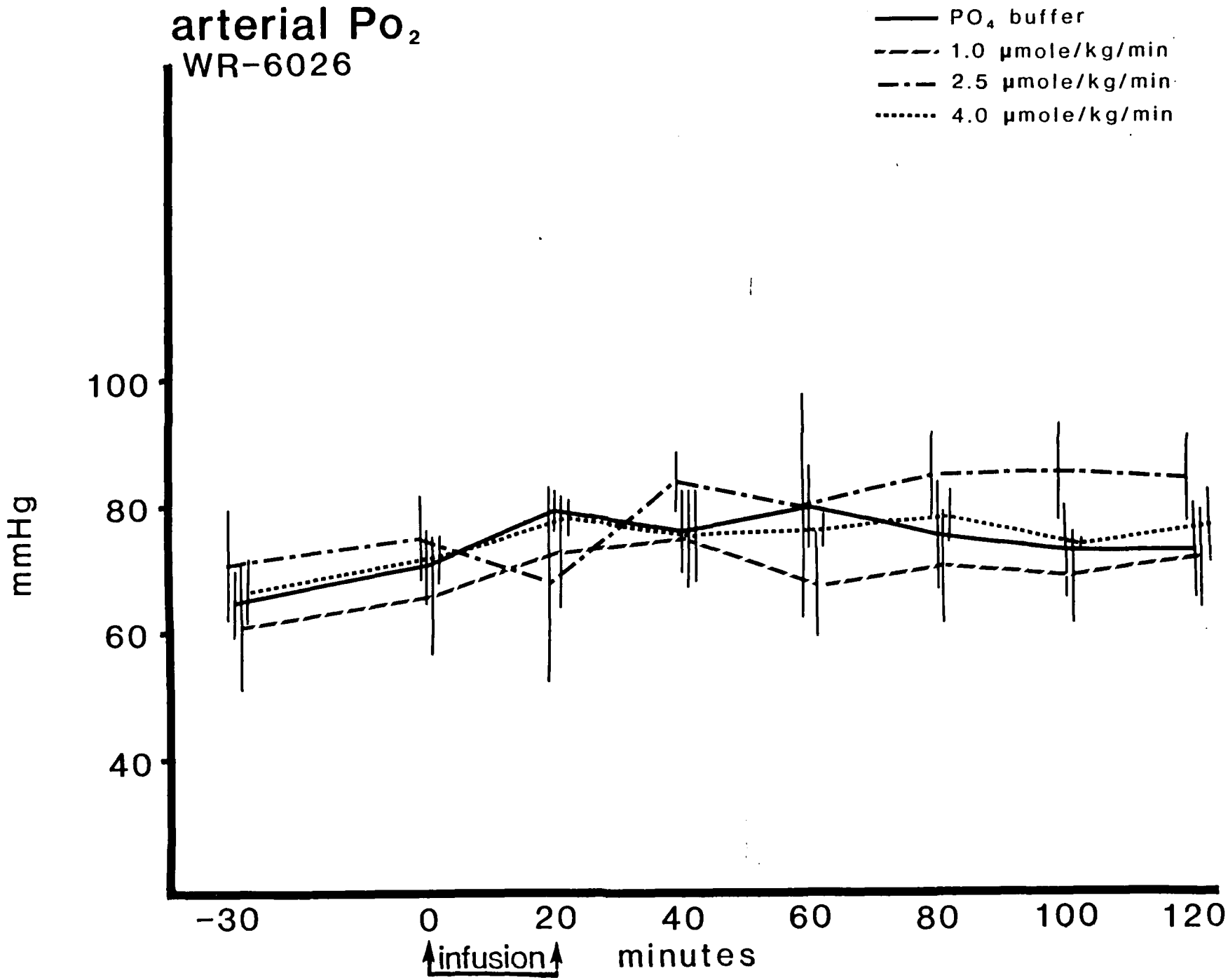

arterial Po_2
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
mmHg
100
80
60
40
-30
0
20
40
60
80
100
120
infusion
minutes

figure 6B

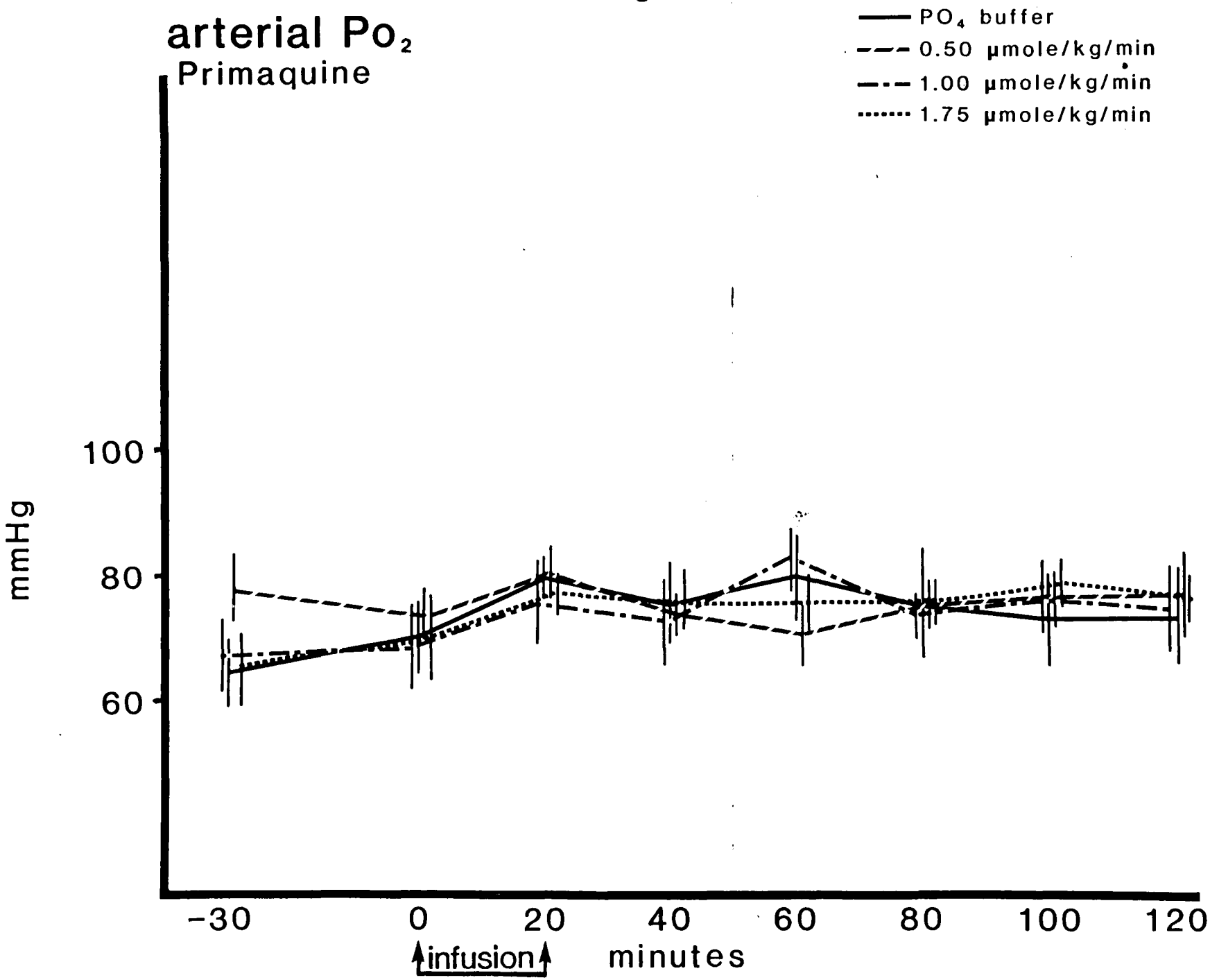

arterial Po_2
Primaquine
PO_4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
mmHg
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 7A

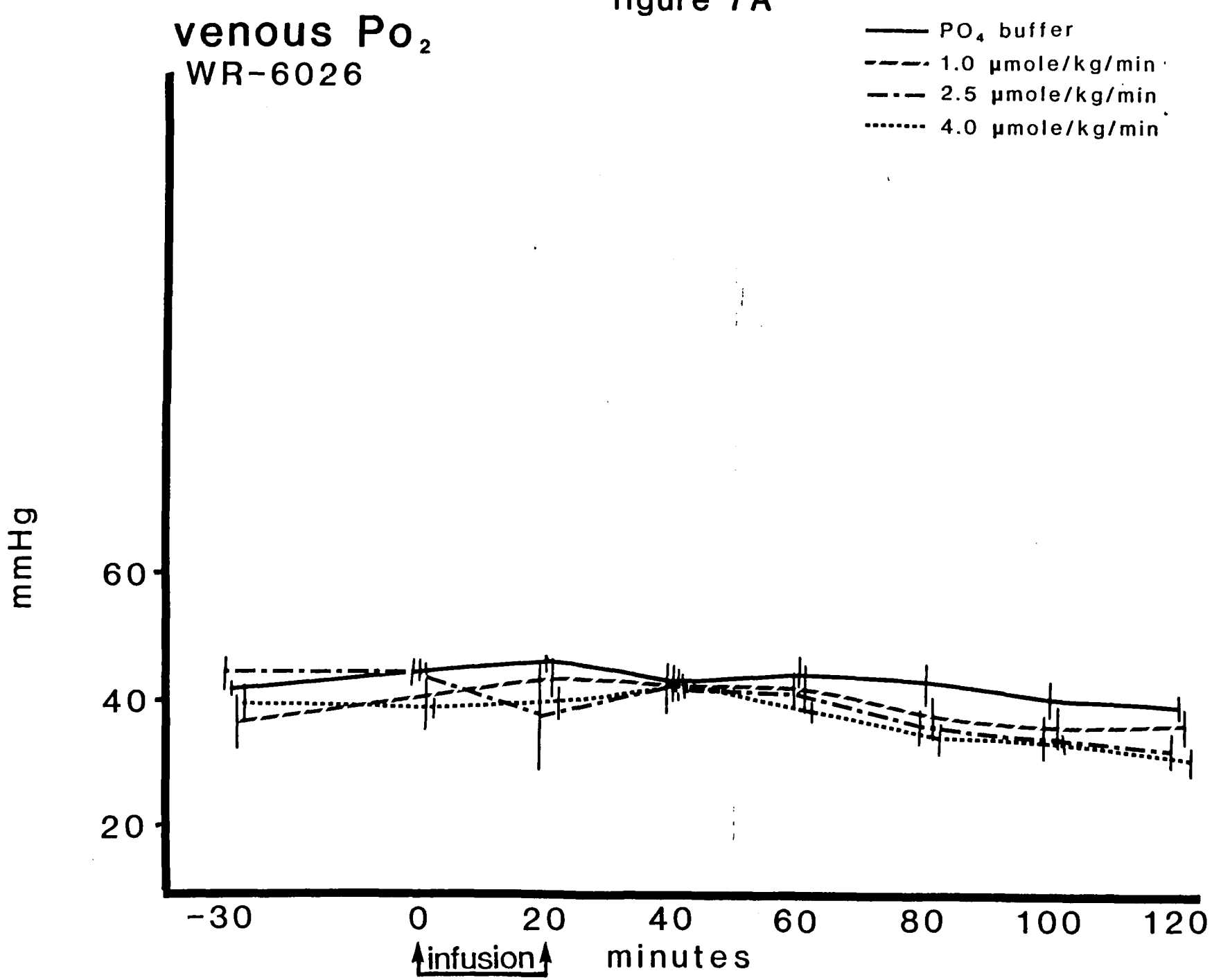

venous Po_2
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
mmHg
60
40
20
-30
0
20
40
60
80
100
120
infusion
minutes

figure 7B

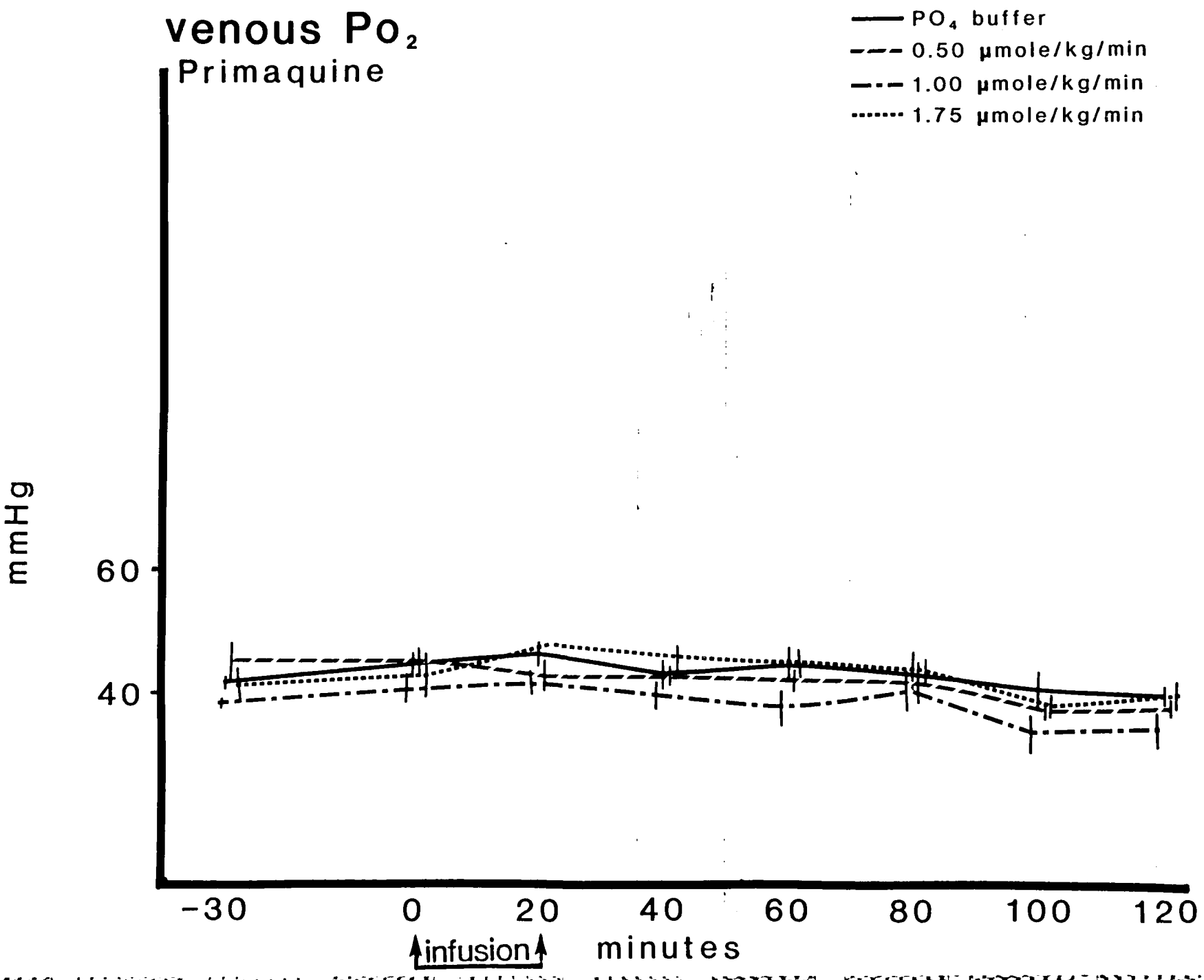

venous Po_2
Primaquine
PO_4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
mmHg
60
40
-30
0
20
40
60
80
100
120
infusion
minutes

figure 8A

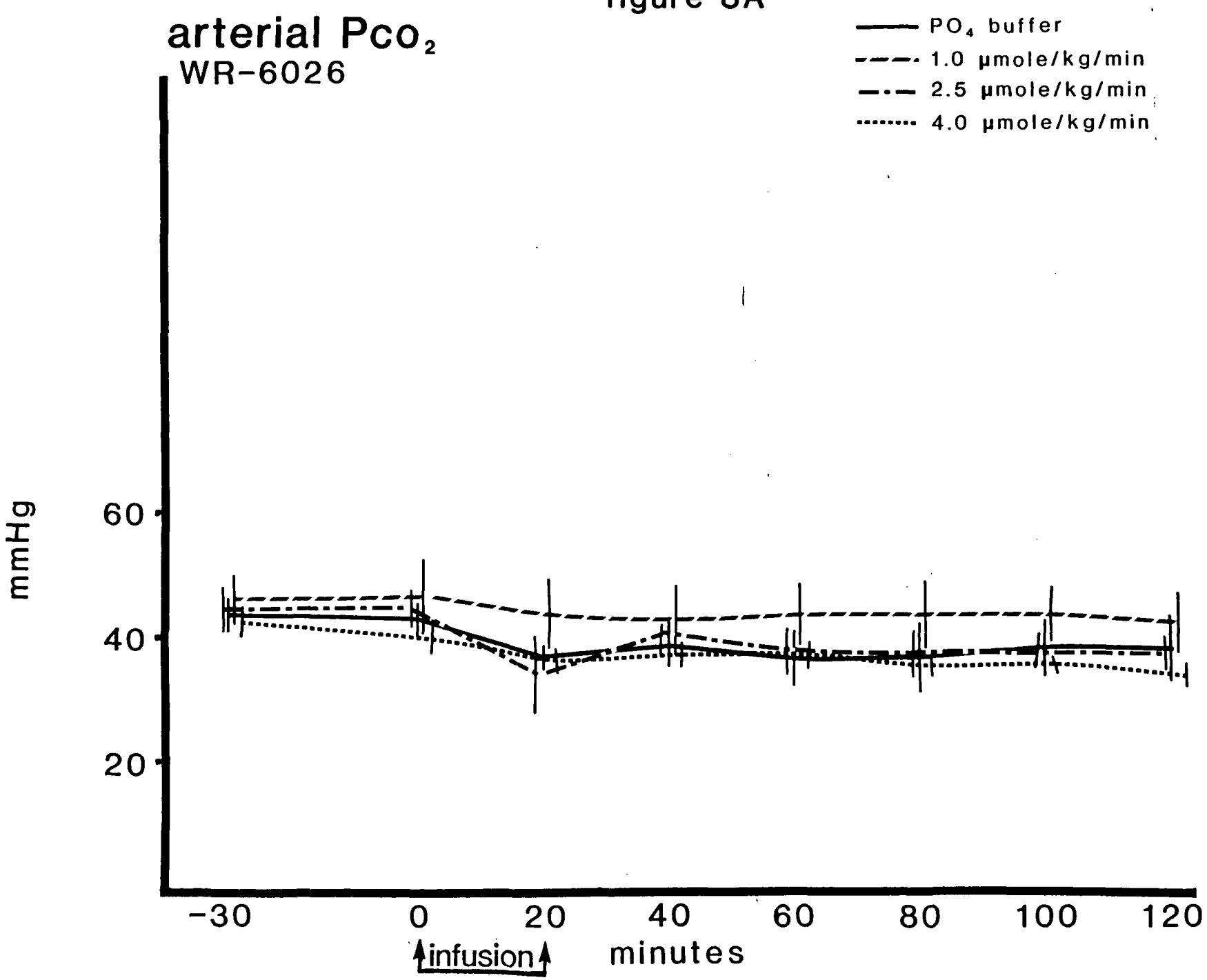

arterial Pco_2
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
mmHg
60
40
20
-30
0
20
40
60
80
100
120
infusion
minutes

figure 8B

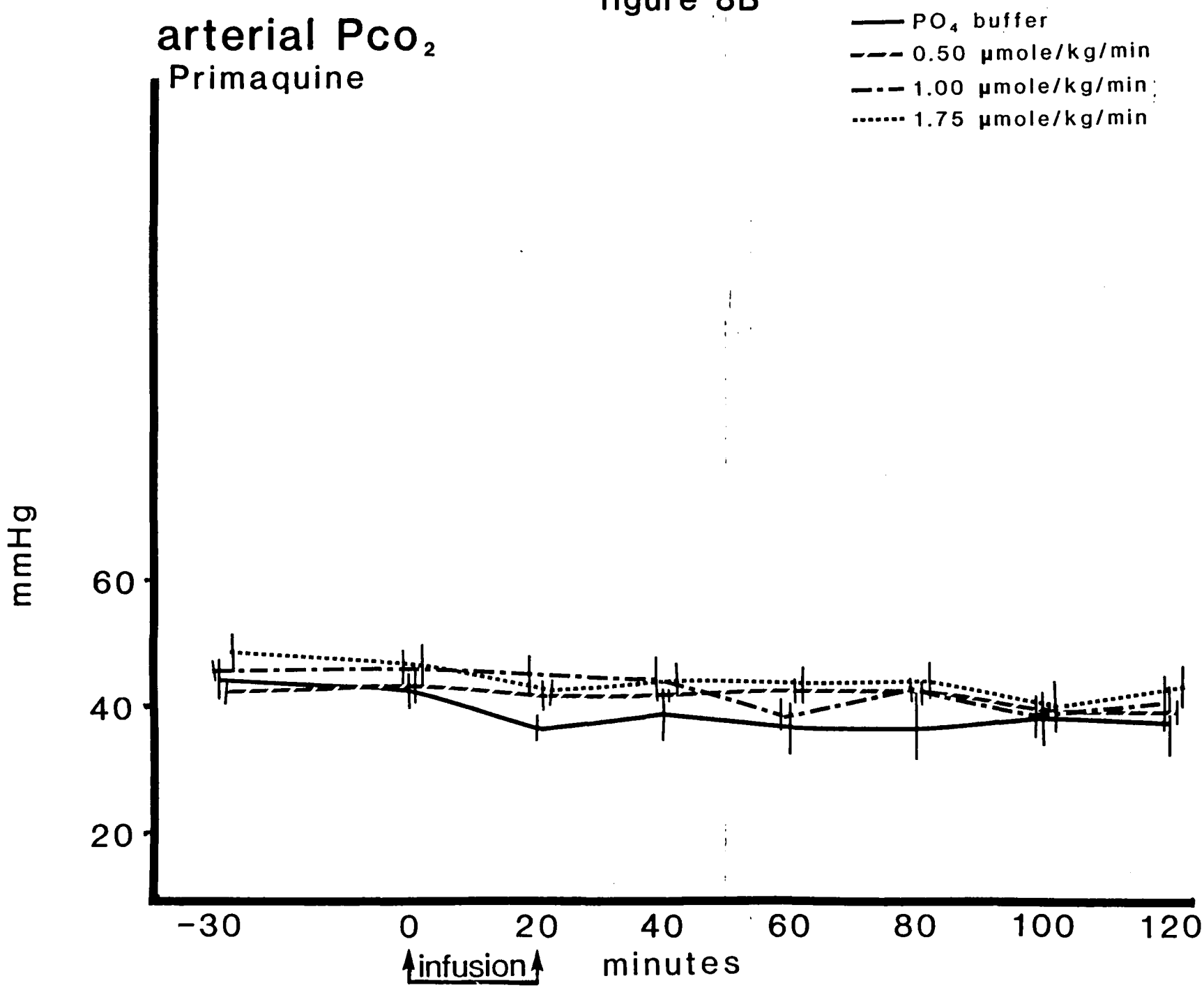

arterial Pco_2
Primaquine
PO_4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
mmHg
60
40
20
-30
0
20
40
60
80
100
120
infusion
minutes

figure 9A

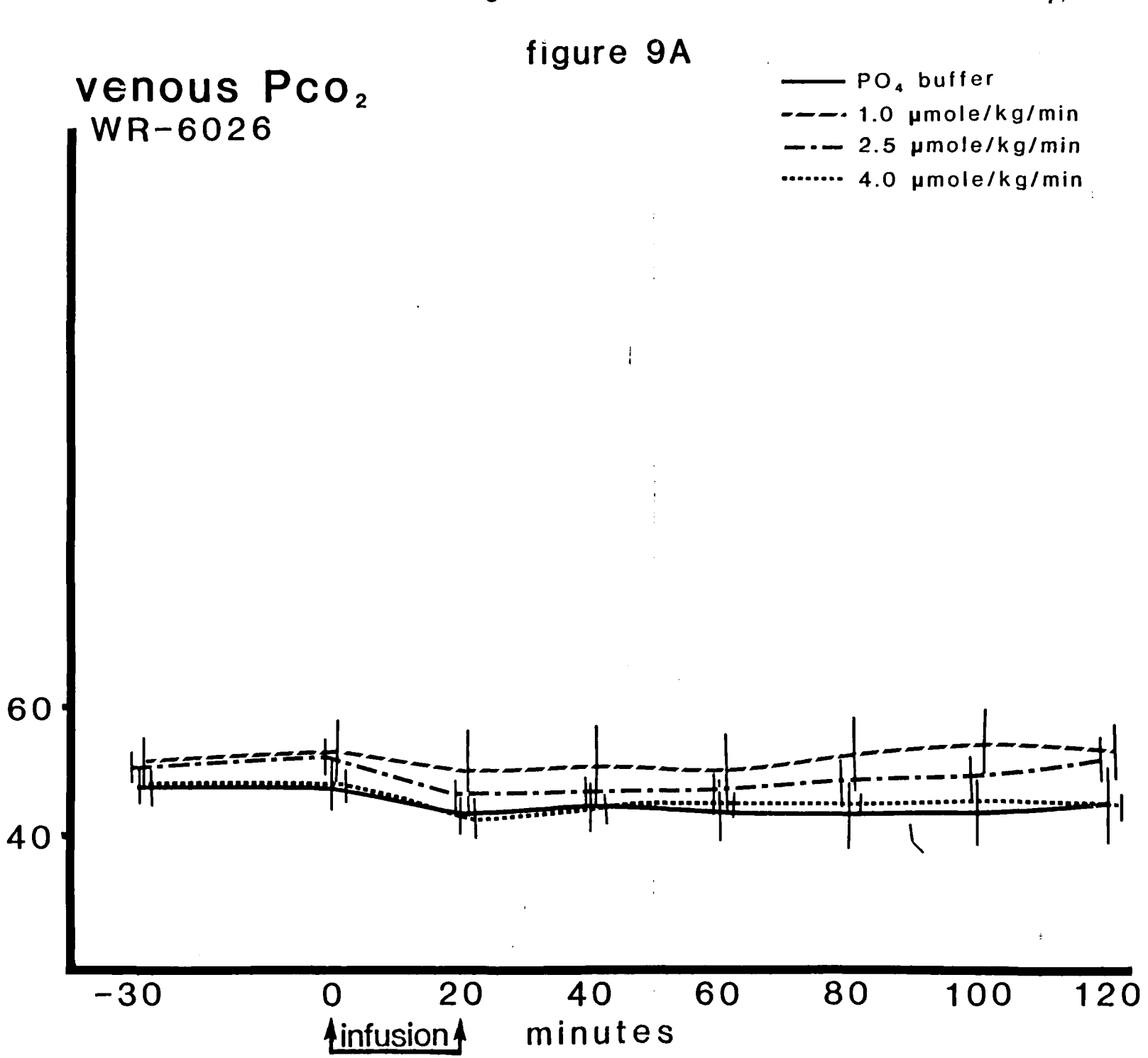

venous Pco_2
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
mmHg
60
40
-30
0
20
40
60
80
100
120
infusion
minutes

figure 9B

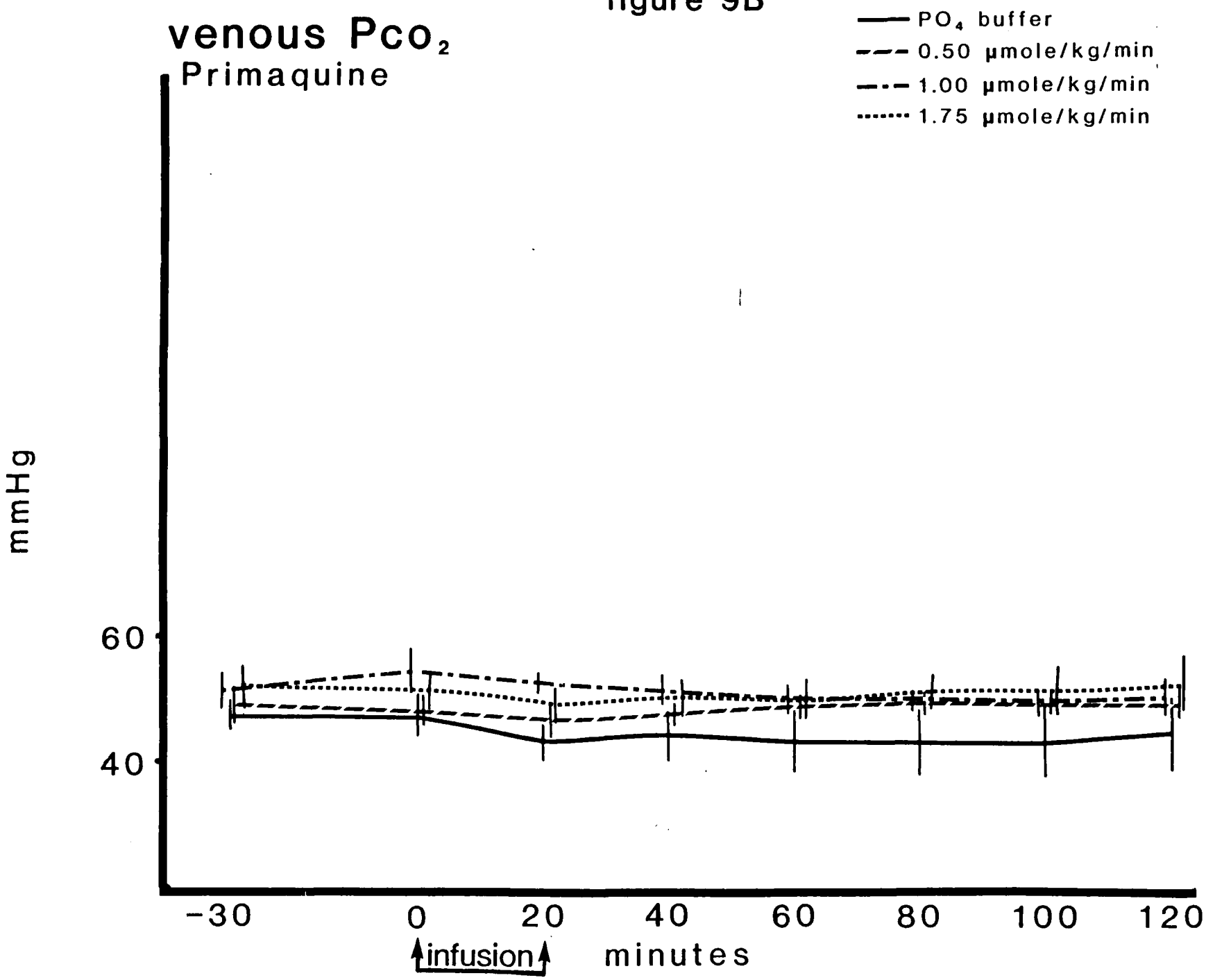

venous Pco2
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
mmHg
60
40
-30
0
20
40
60
80
100
120
infusion
minutes

figure 10A

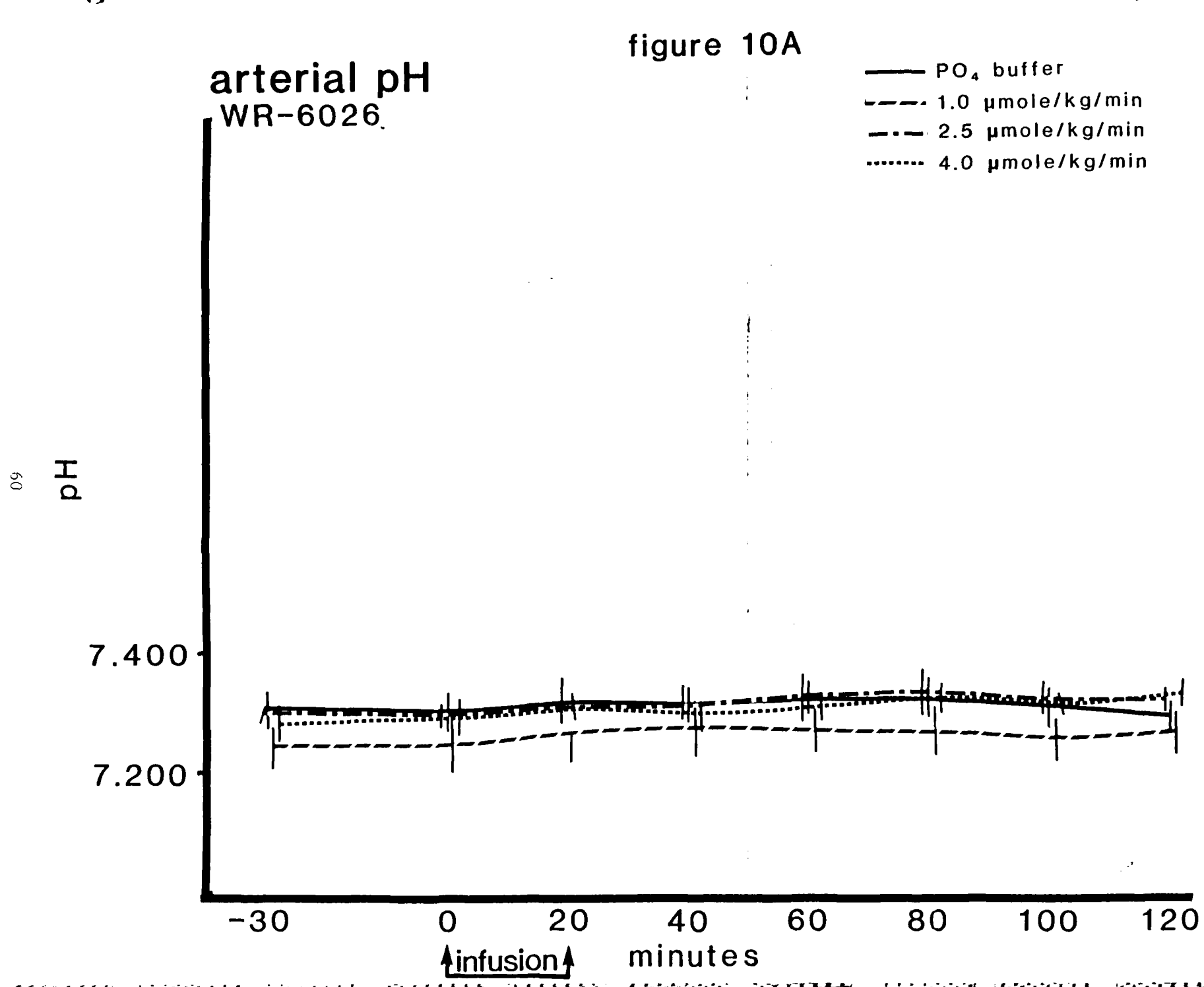

arterial pH
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
pH
7.400
7.200
-30
0
20
40
60
80
100
120
infusion
minutes

figure 10B

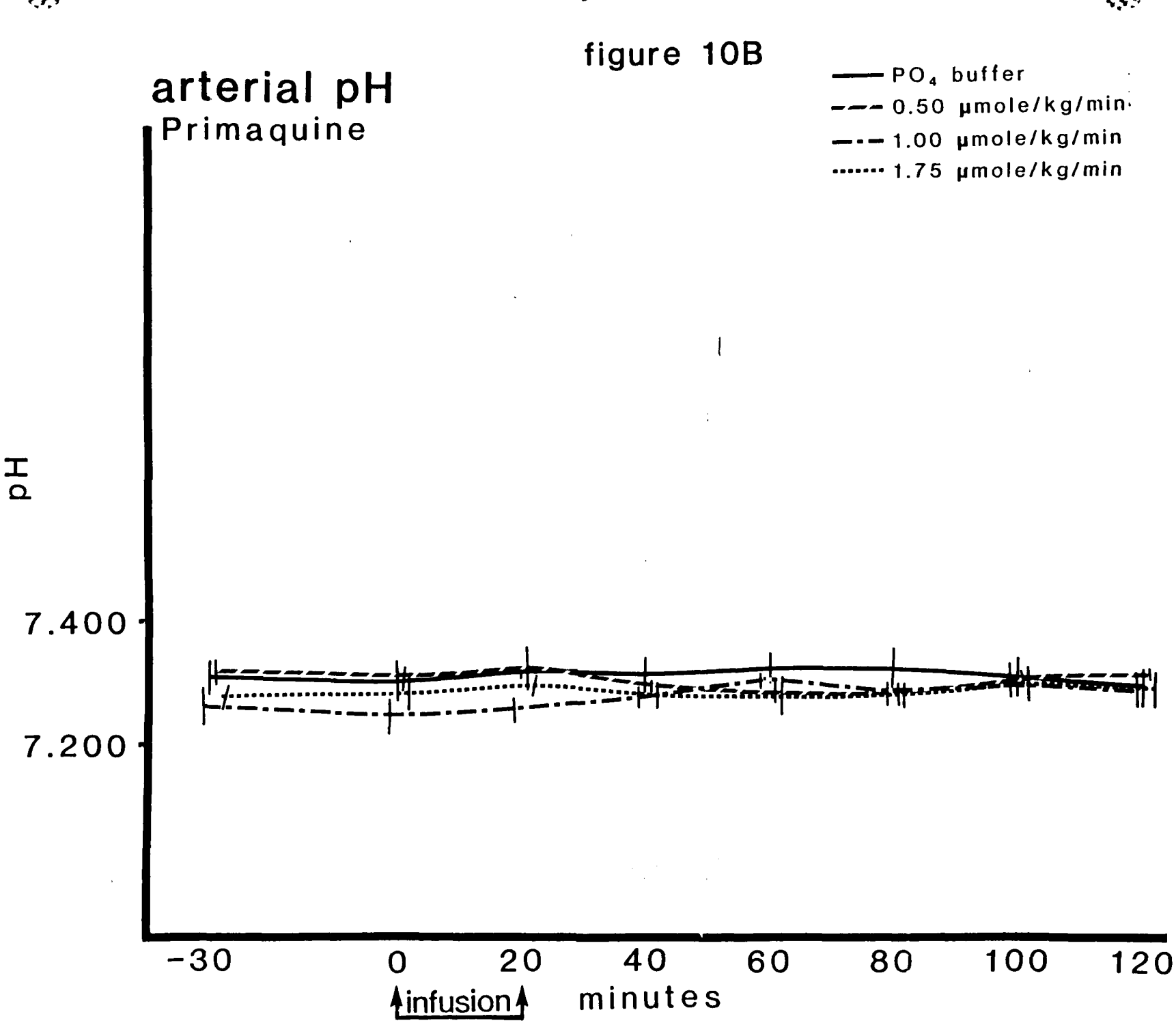

arterial pH
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
pH
7.400
7.200
-30
0
20
40
60
80
100
120
infusion
minutes

figure 11A

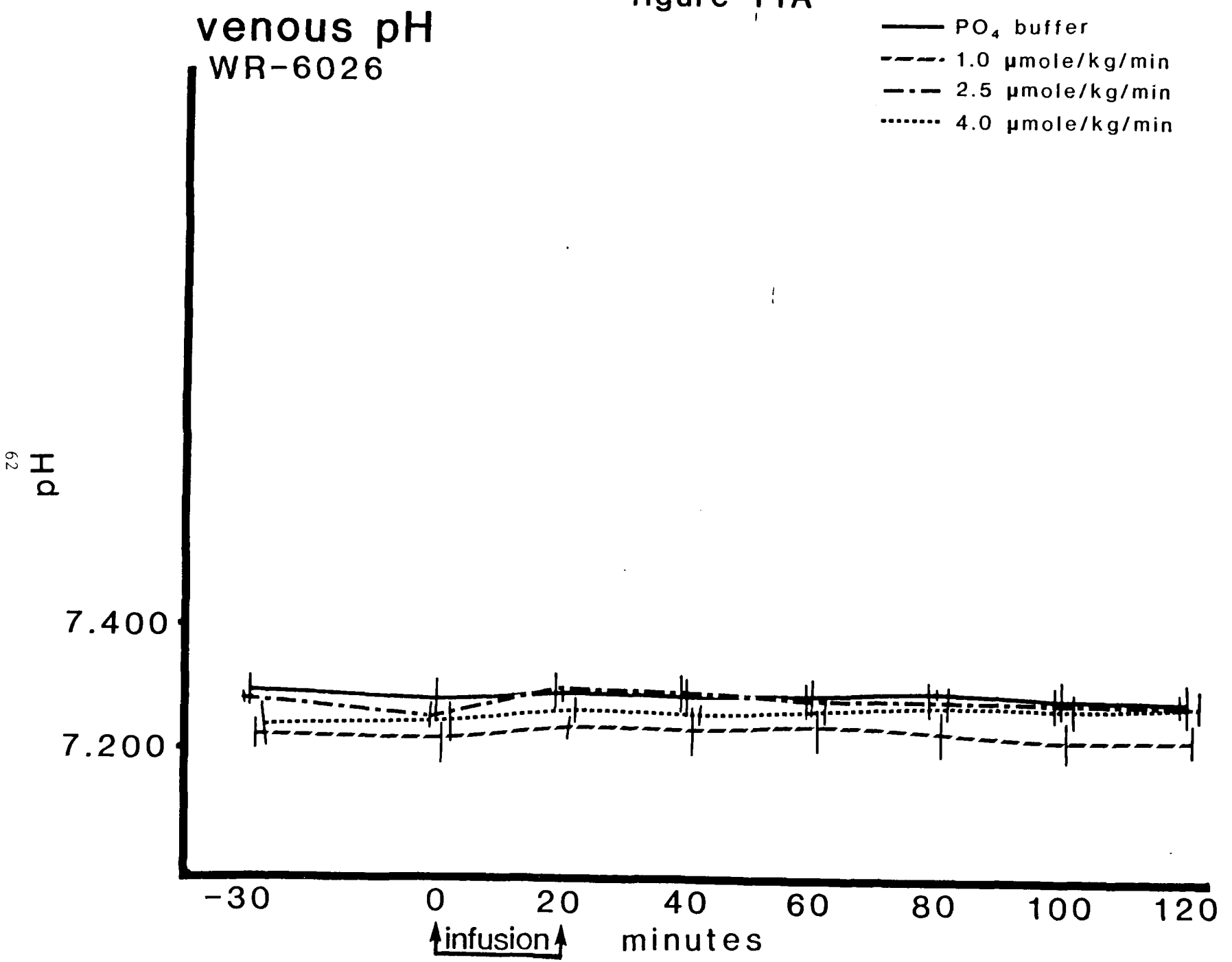

venous pH
WR-6026
PO_4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
pH
7.400
7.200
-30
0
20
40
60
80
100
120
infusion
minutes

figure 11B

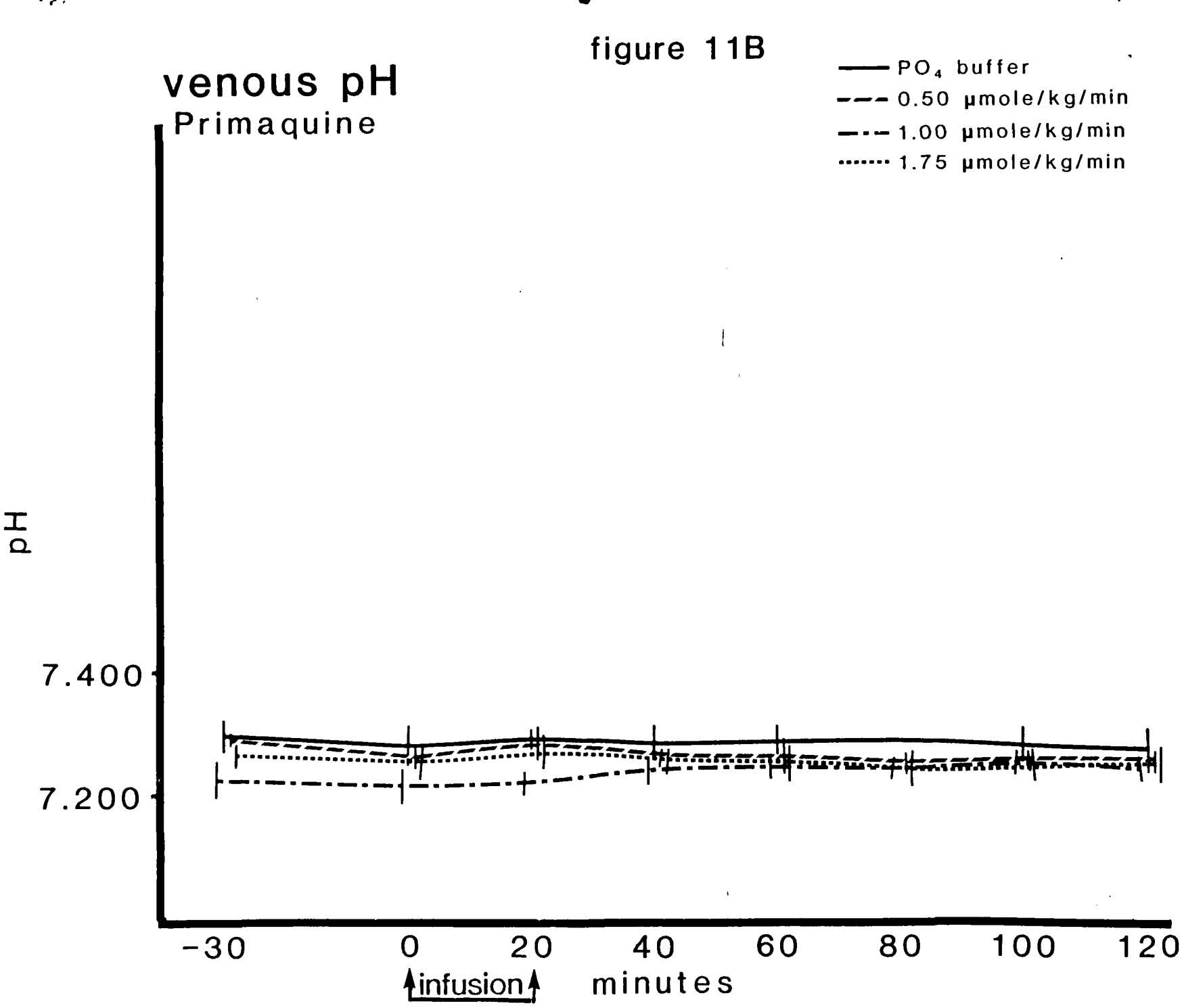

venous pH
Primaquine
PO_4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
pH
7.400
7.200
-30
0
20
40
60
80
100
120
infusion
minutes

figure 12A

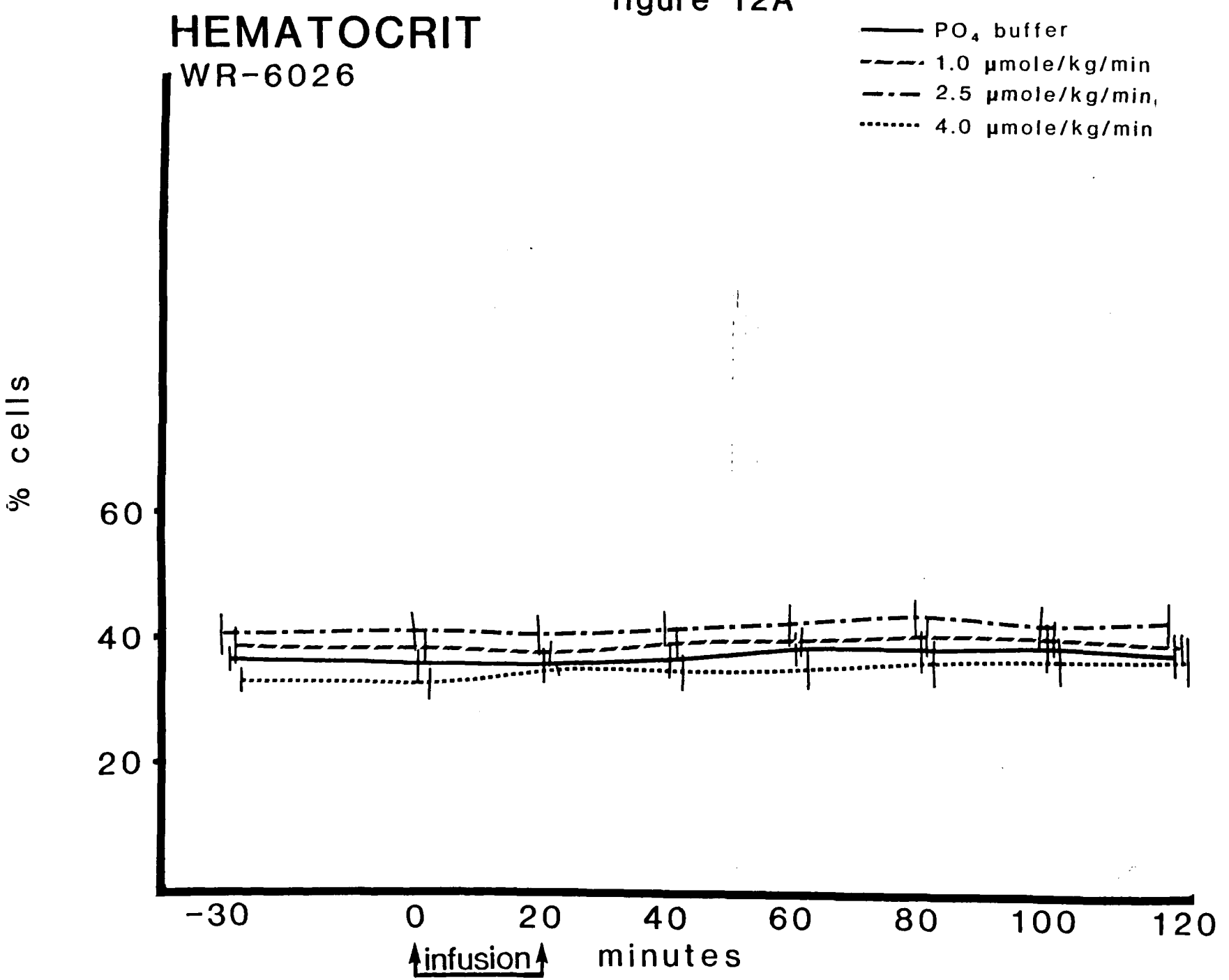

HEMATOCRIT
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% cells
60
40
20
-30
0
20
40
60
80
100
120
infusion
minutes

figure 12B

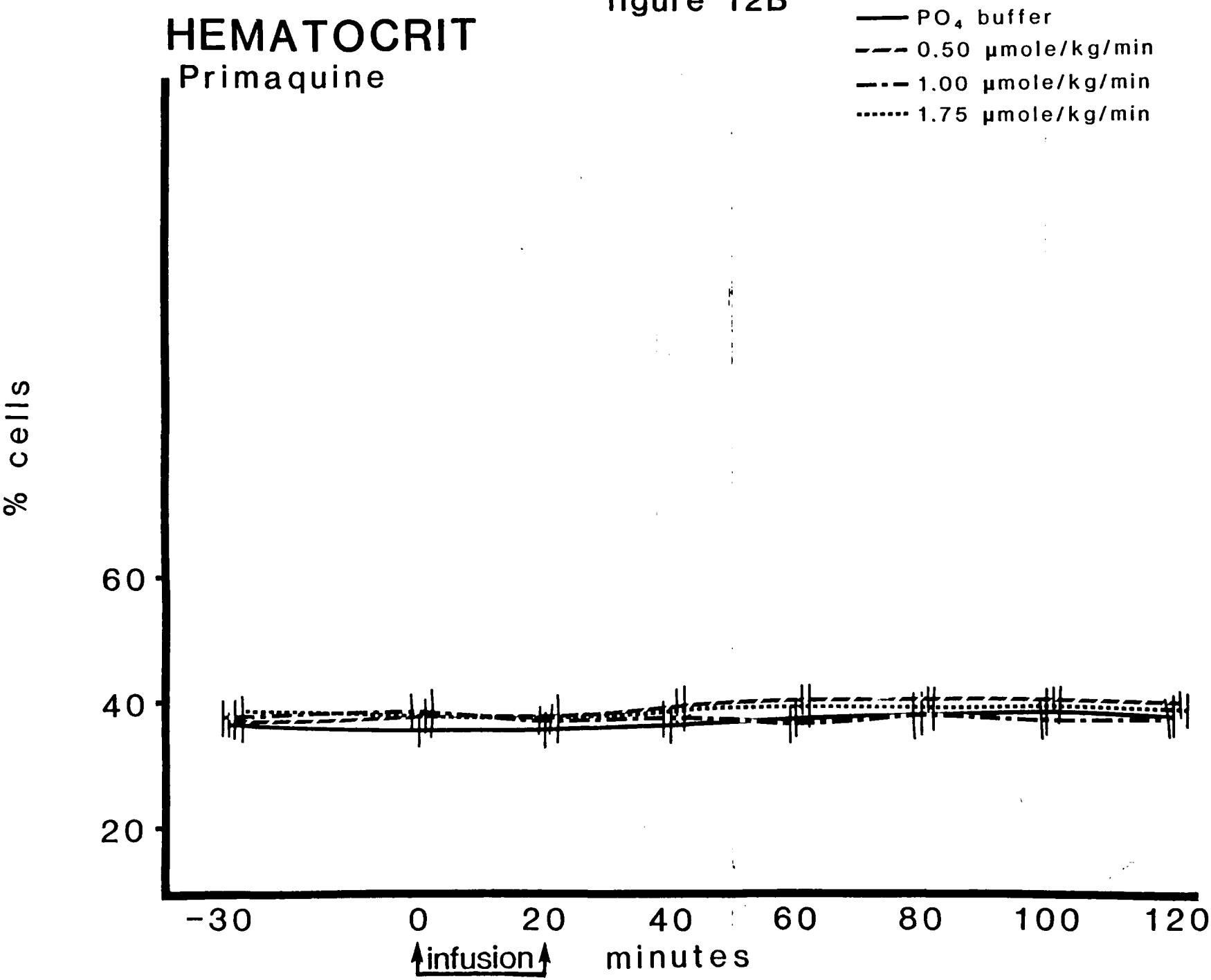

HEMATOCRIT
Primaquine
PO_4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% cells
60
40
20
-30
0
20
40
60
80
100
120
infusion
minutes

figure 13A

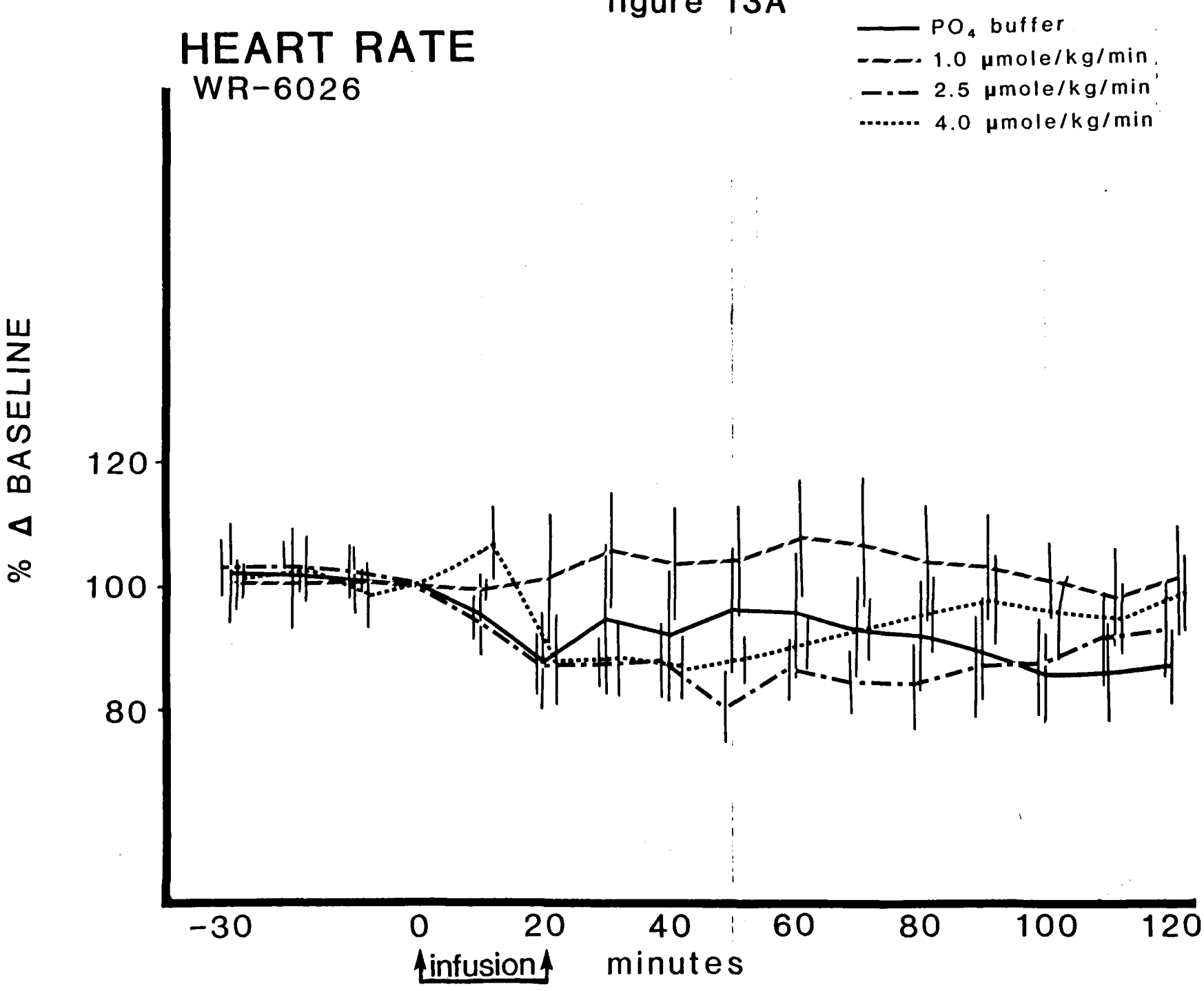

HEART RATE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 13B

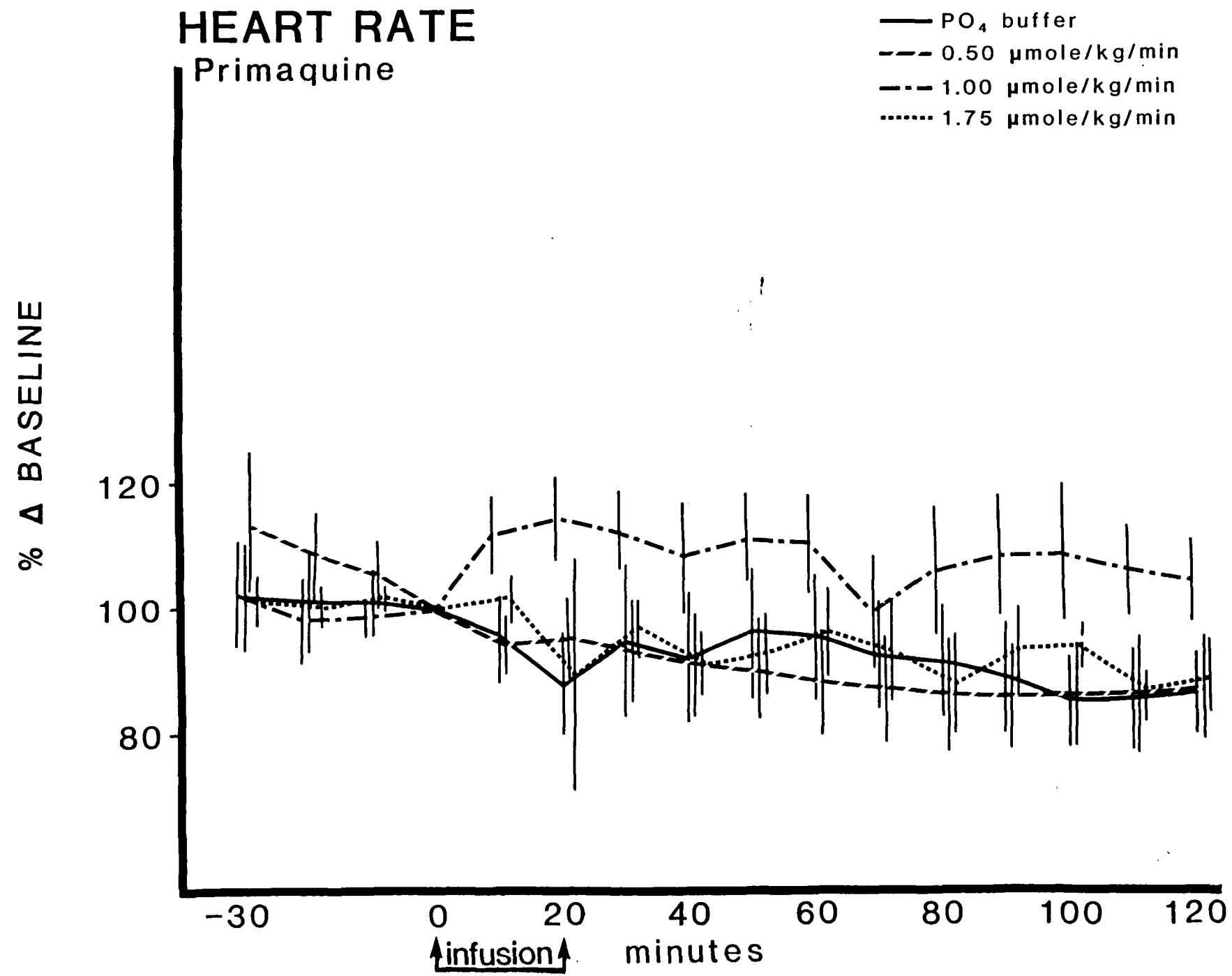

HEART RATE
Primaquine
PO_4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 14A

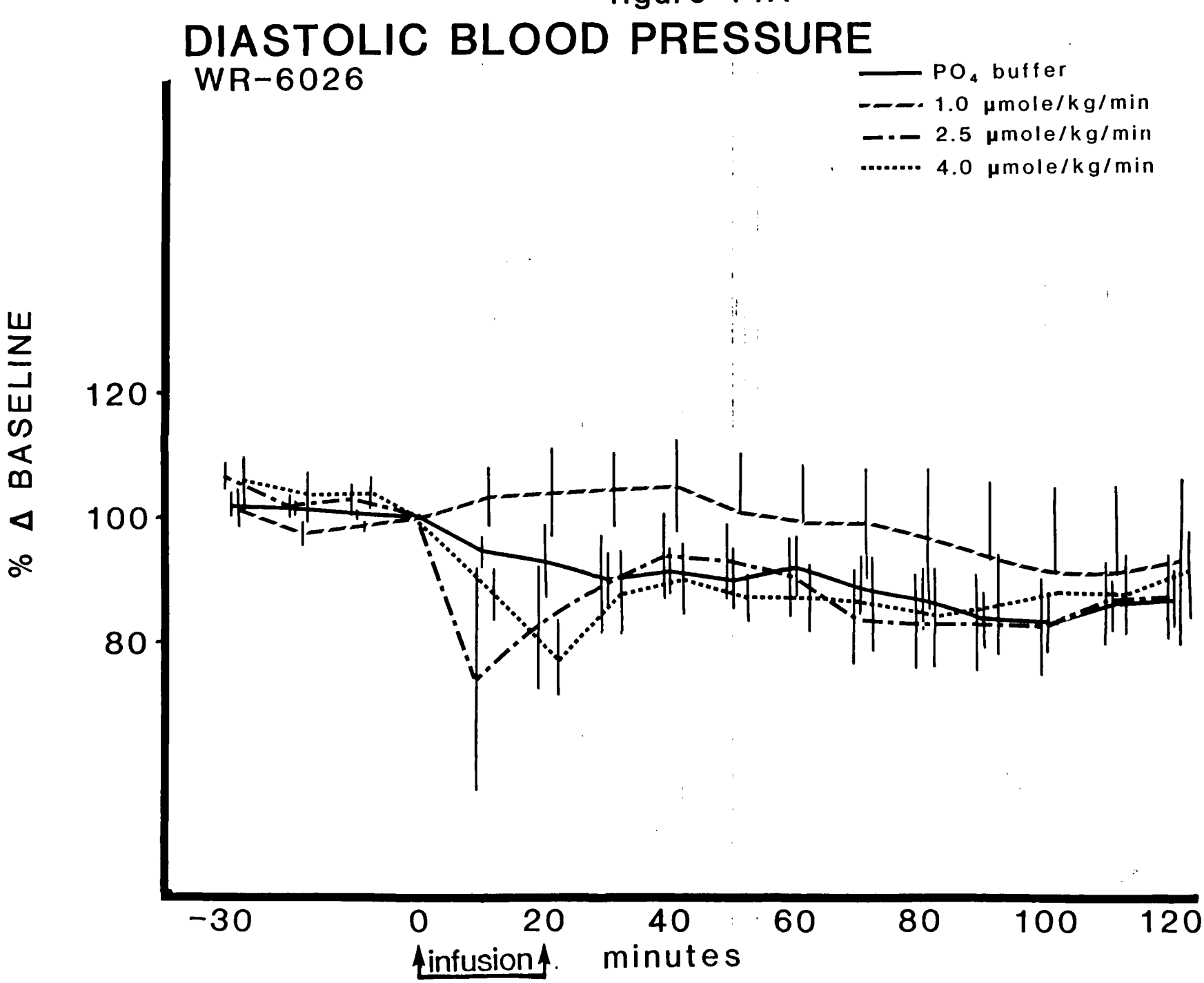

DIASTOLIC BLOOD PRESSURE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 14B

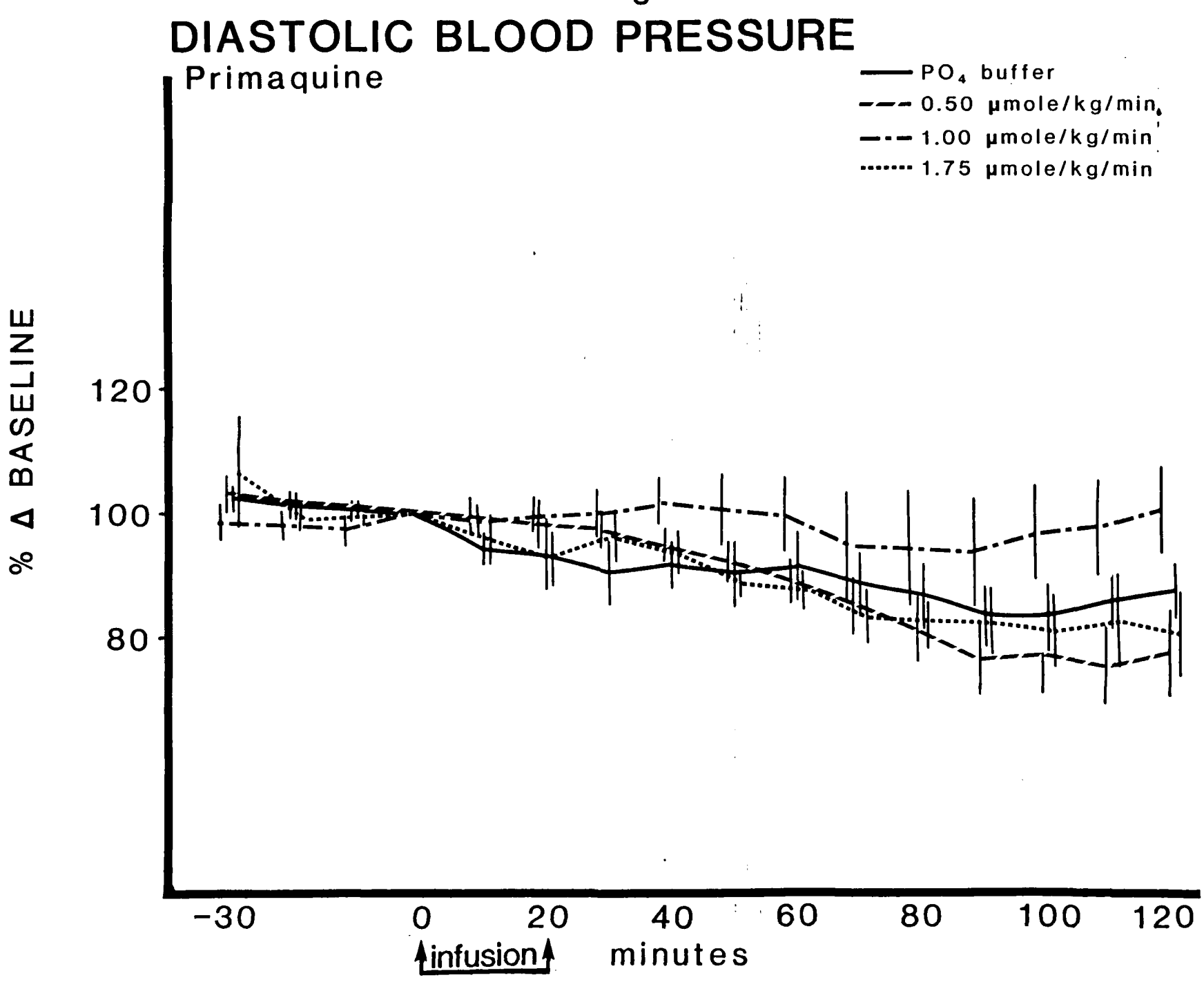

DIASTOLIC BLOOD PRESSURE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 15A

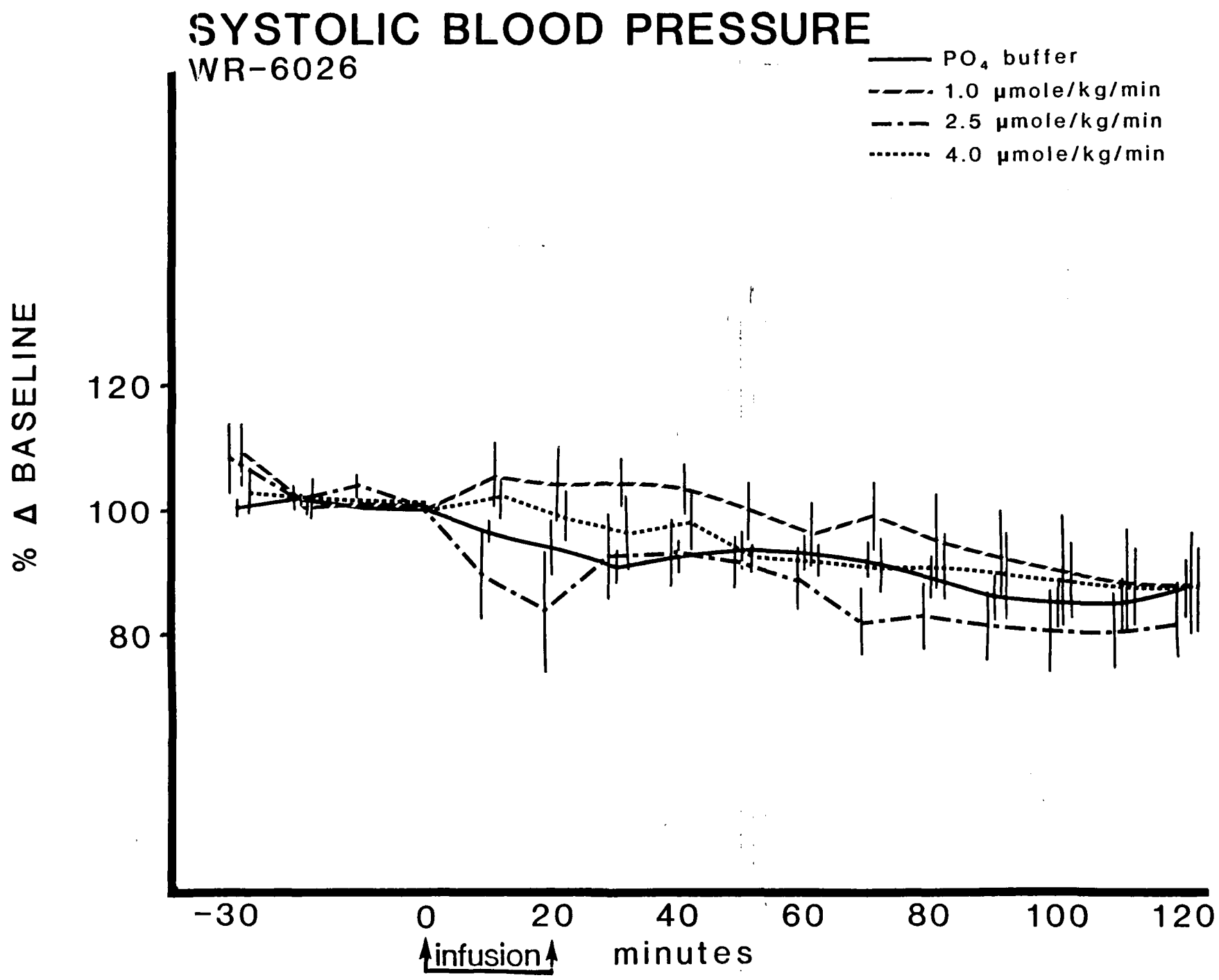

SYSTOLIC BLOOD PRESSURE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 15B

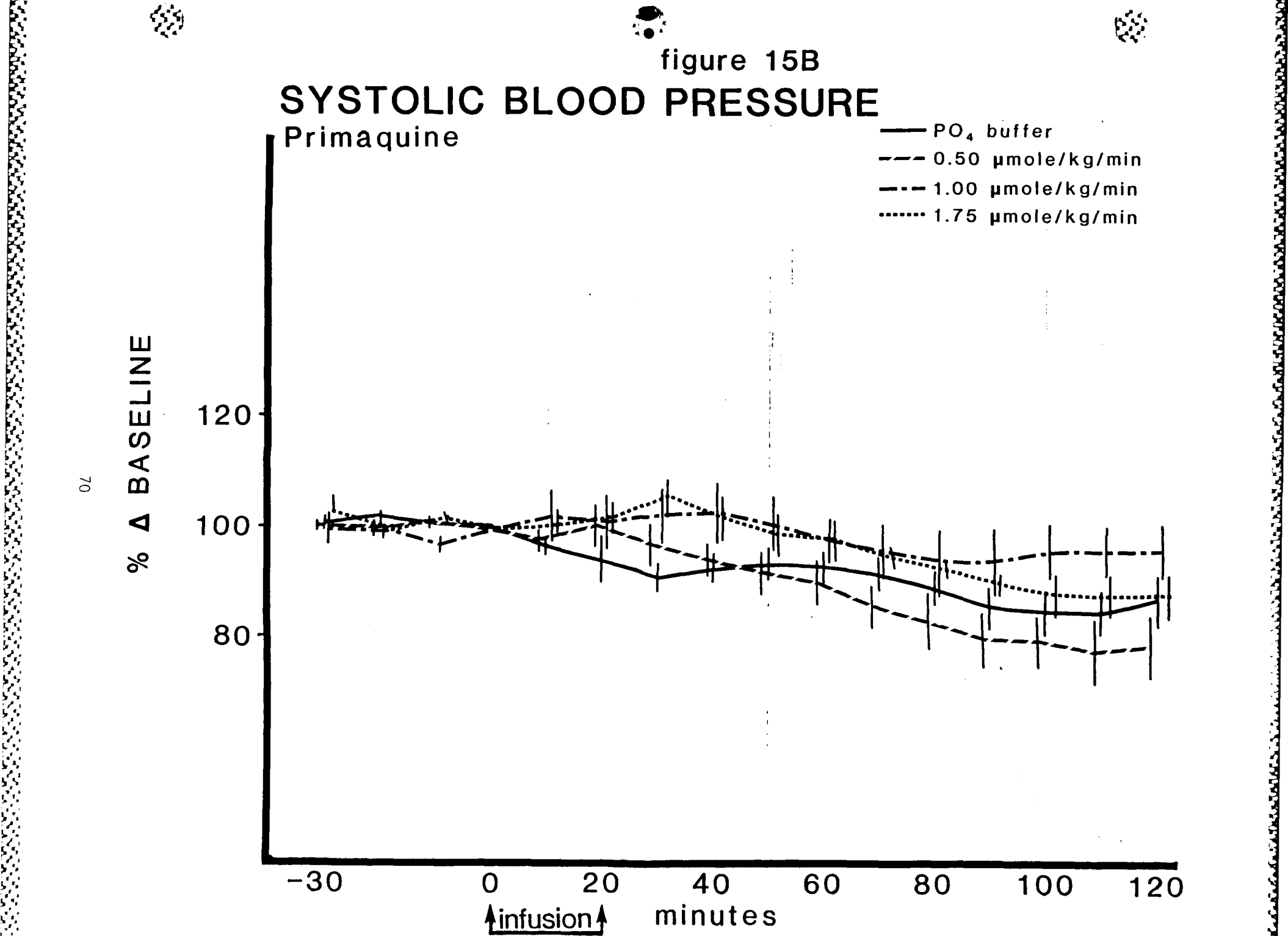

SYSTOLIC BLOOD PRESSURE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
120
100
80
-30
0
20
40
60
80
100
120
infusion
minutes

figure 16A

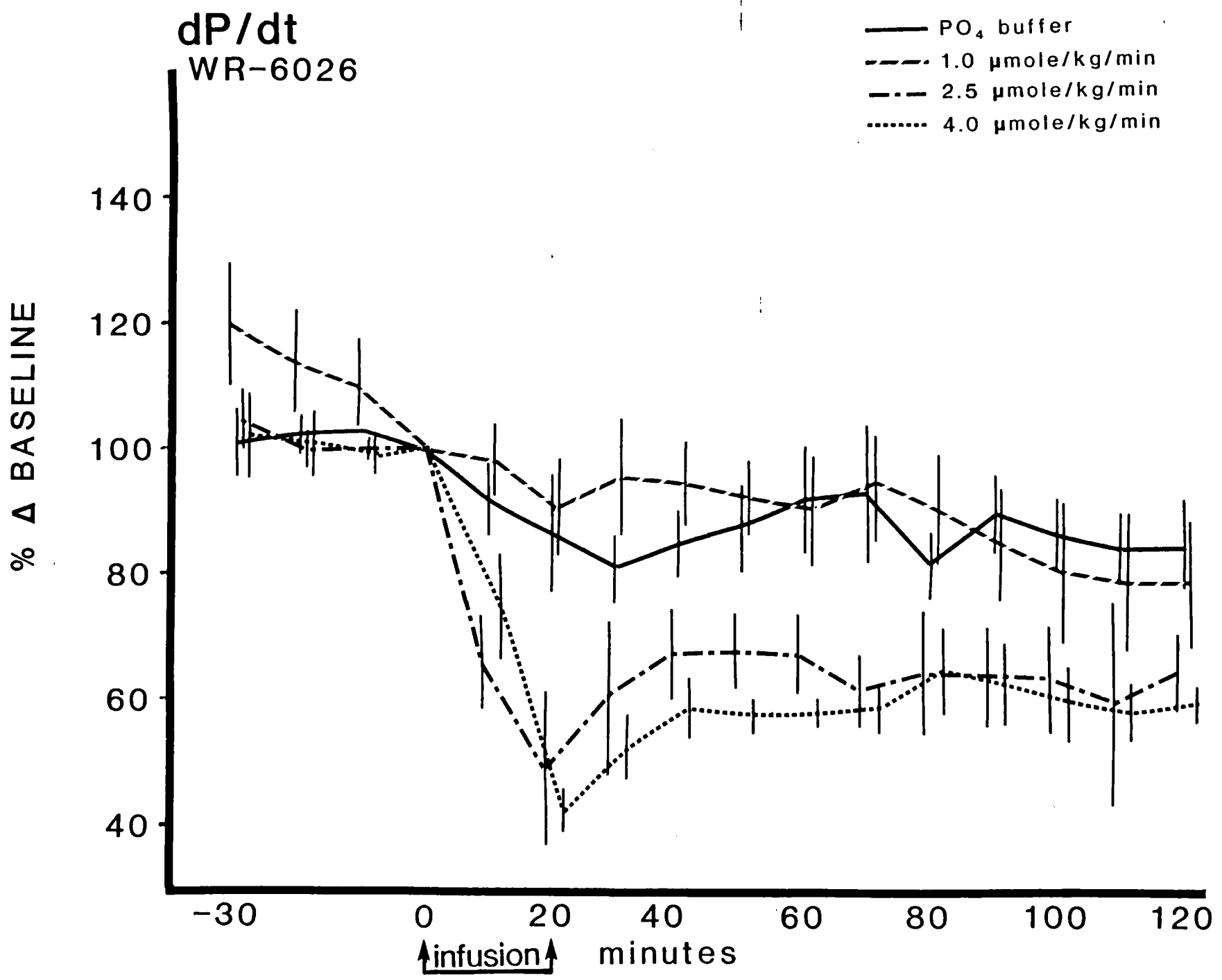

dP/dt
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
140
120
100
80
60
40
-30
0
20
40
60
80
100
120
infusion
minutes

figure 16B

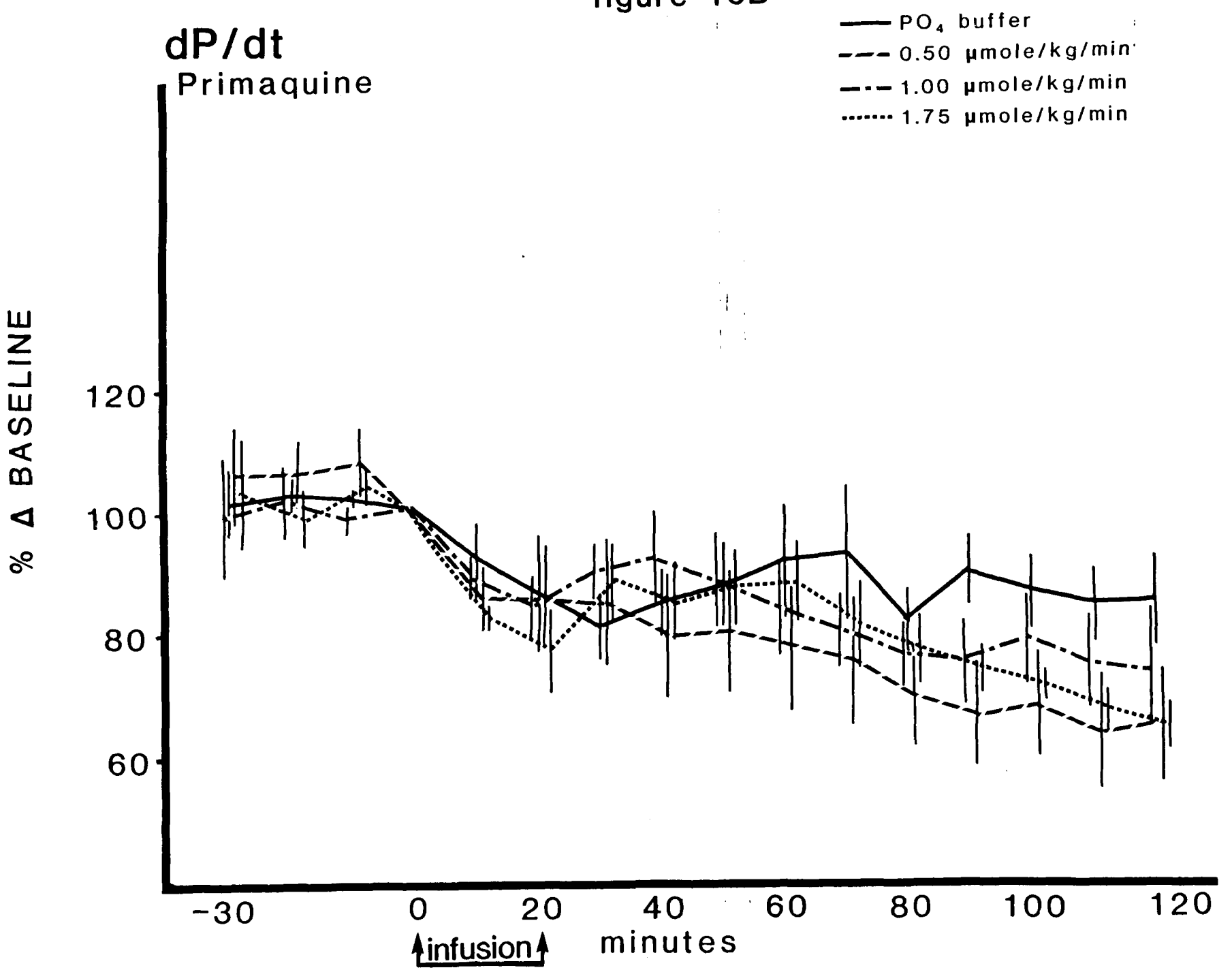

dP/dt
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 17A

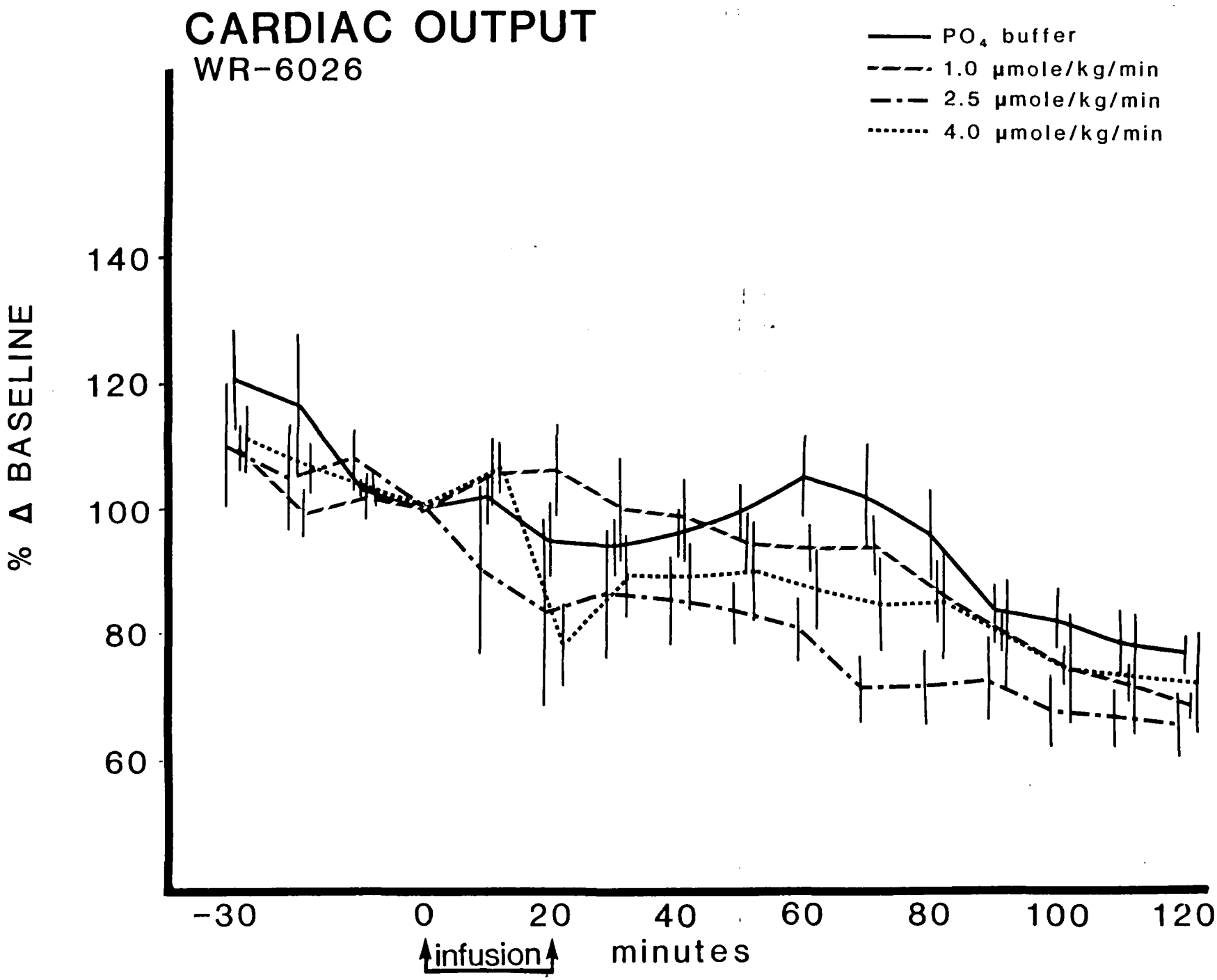

CARDIAC OUTPUT
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 17B

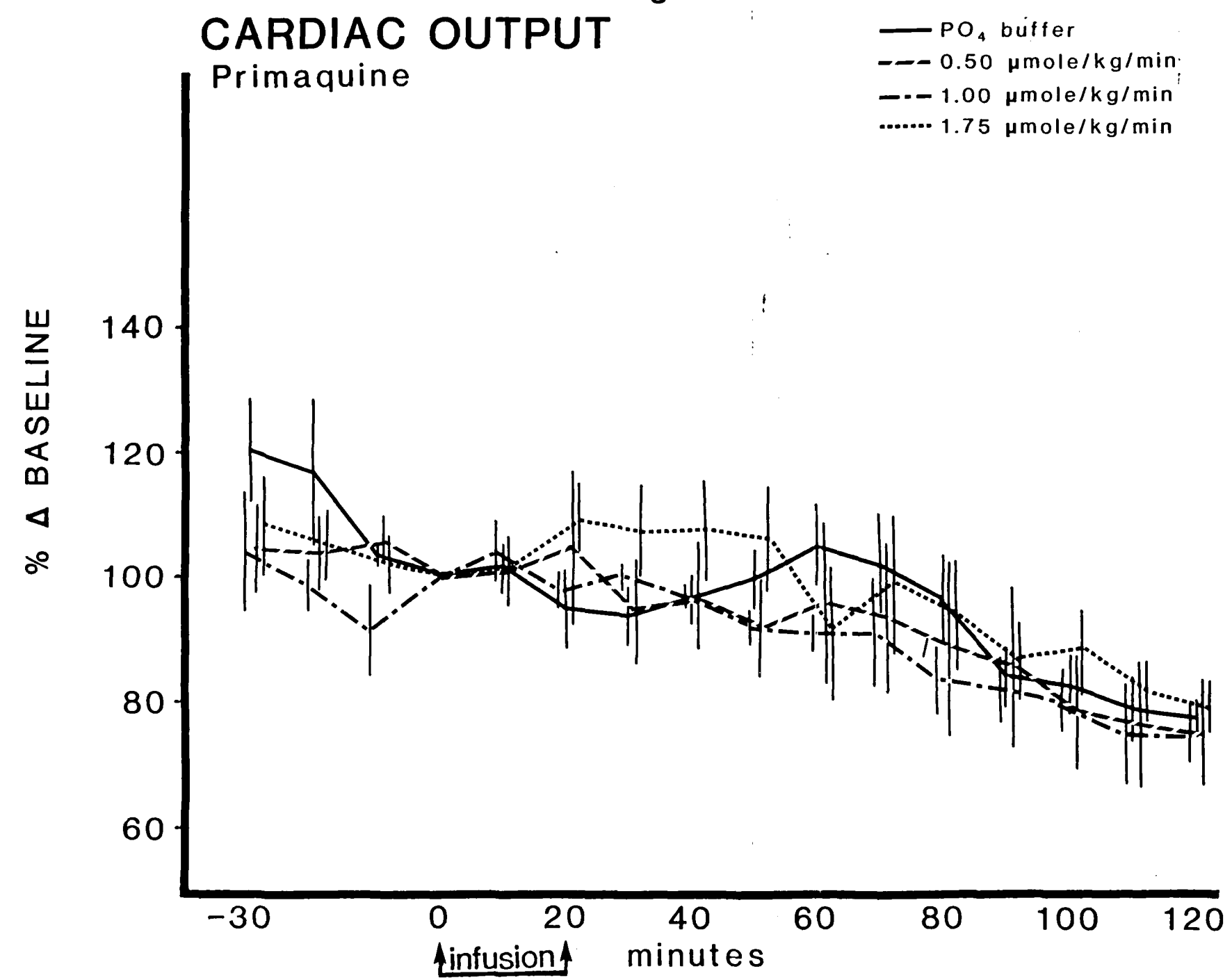

CARDIAC OUTPUT
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 18A

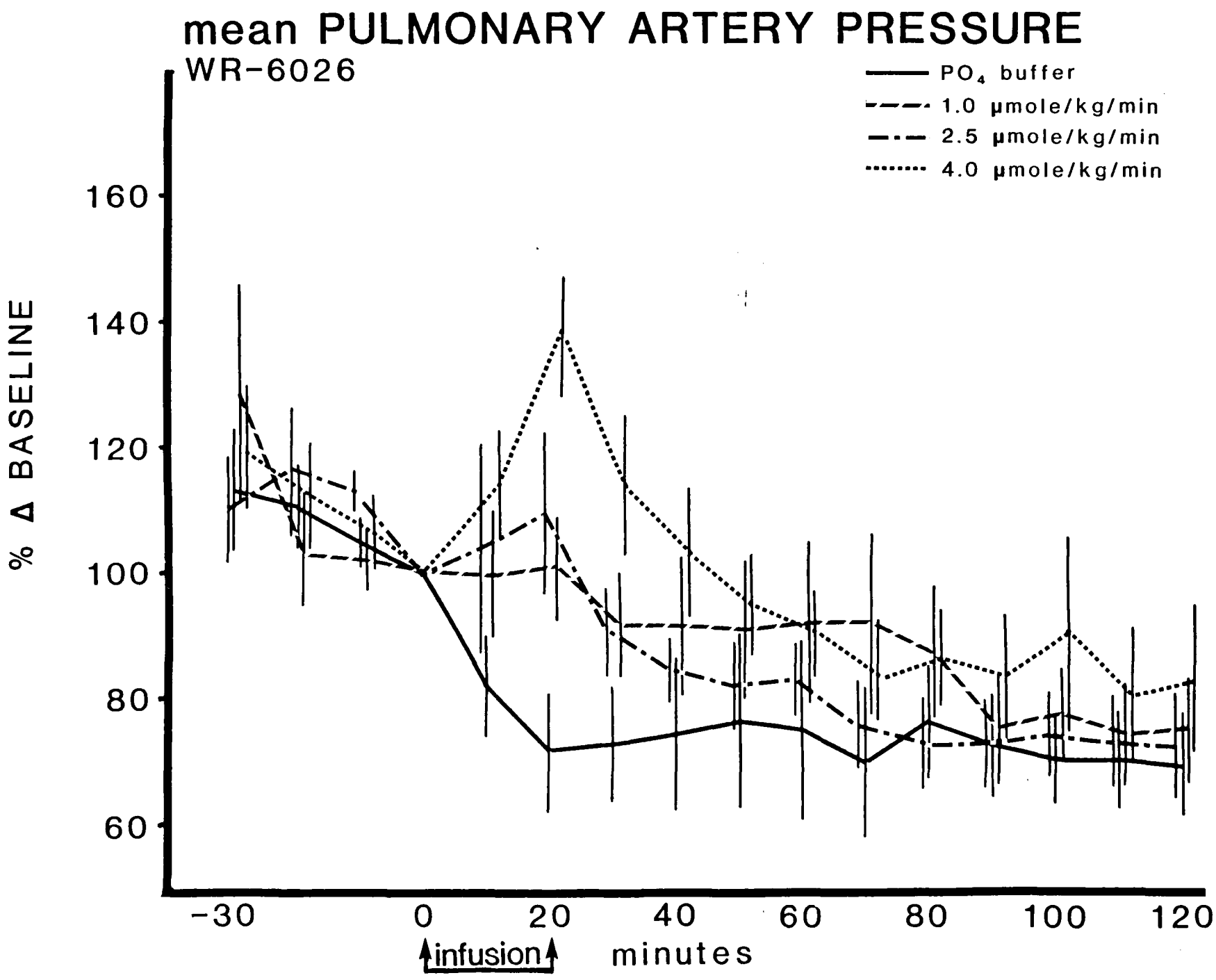

mean PULMONARY ARTERY PRESSURE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
160
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 18B

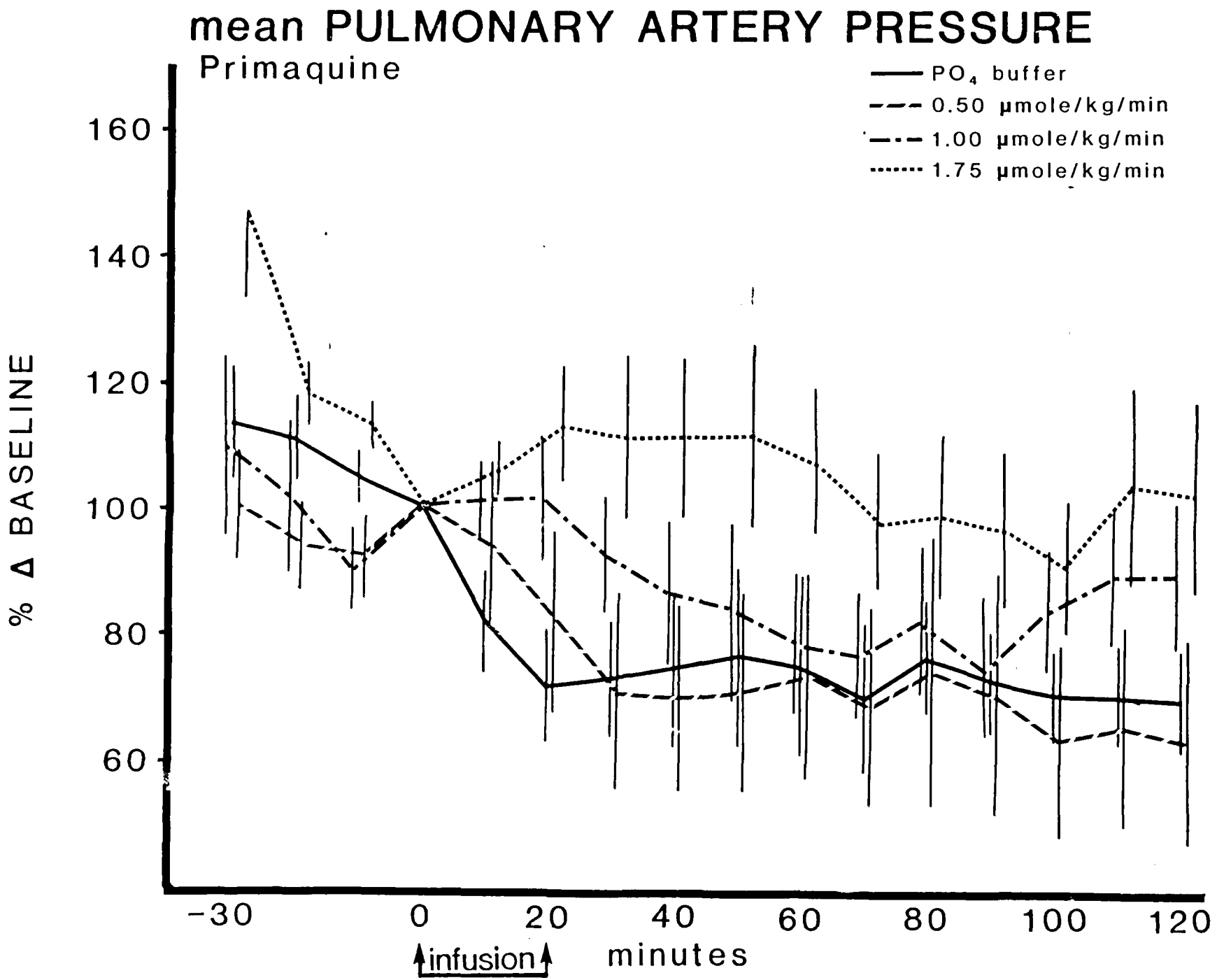

mean PULMONARY ARTERY PRESSURE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
160
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 19A

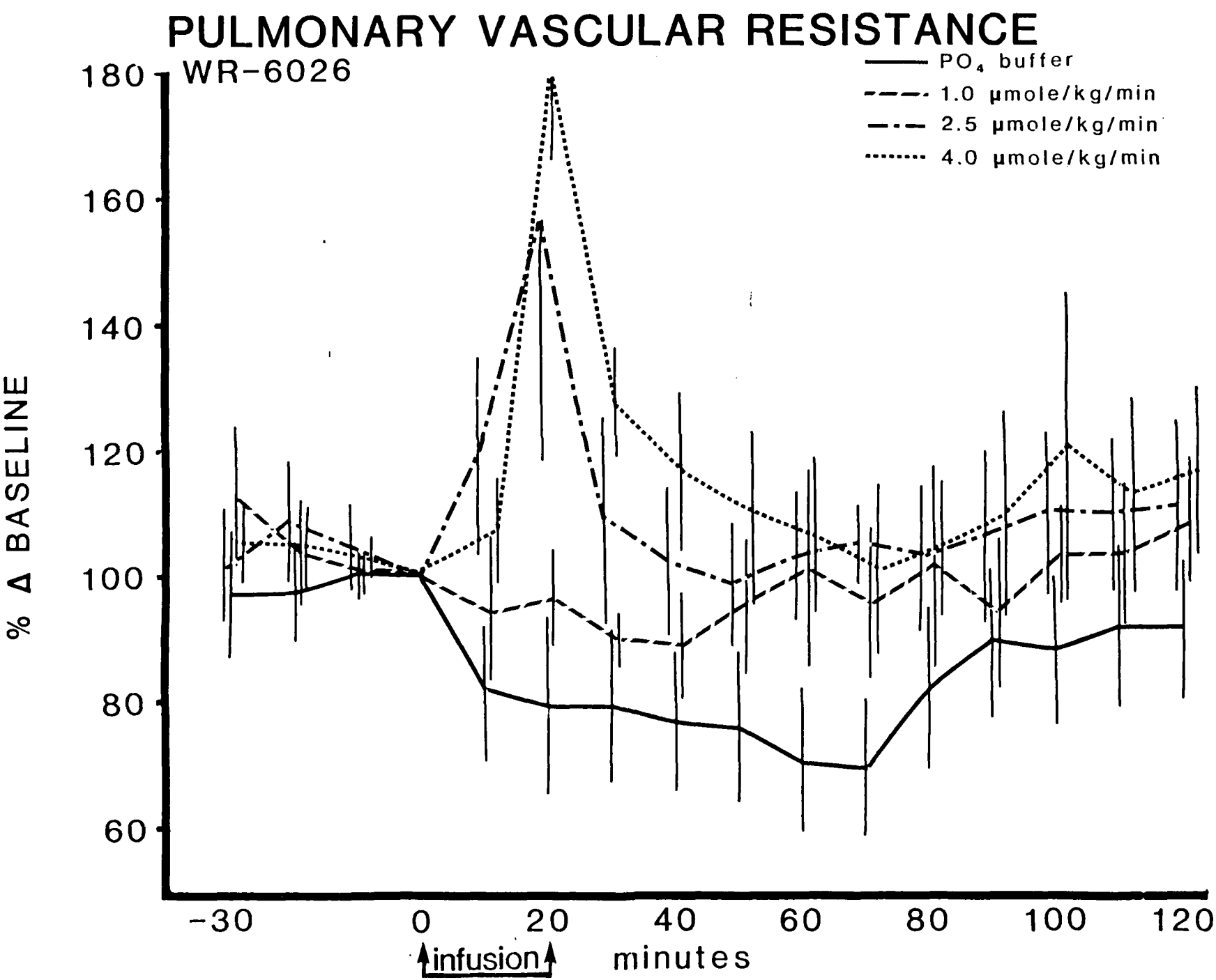

PULMONARY VASCULAR RESISTANCE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
% Δ BASELINE
180
160
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 19B

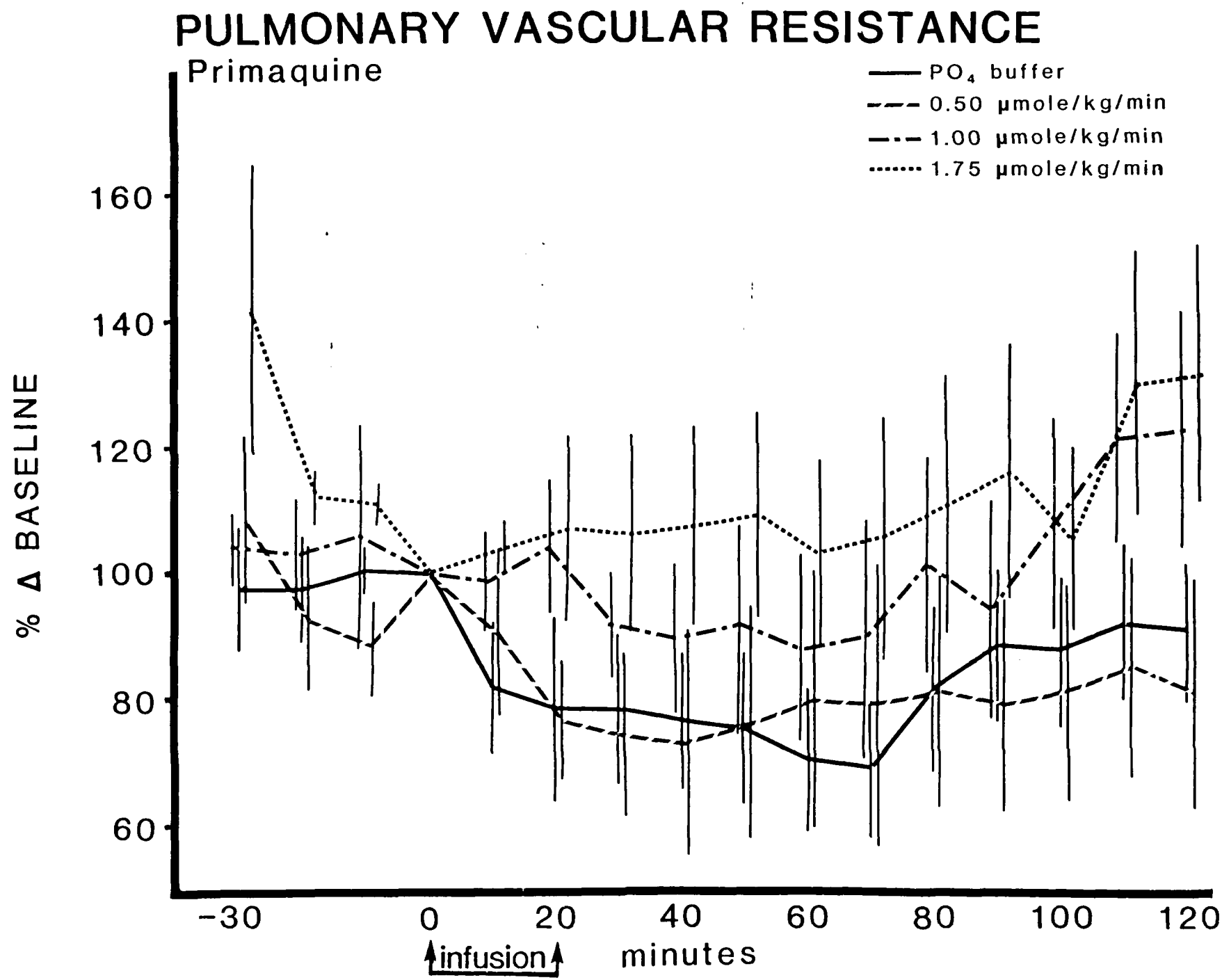

PULMONARY VASCULAR RESISTANCE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
% Δ BASELINE
160
140
120
100
80
60
-30
0
20
40
60
80
100
120
infusion
minutes

figure 20A

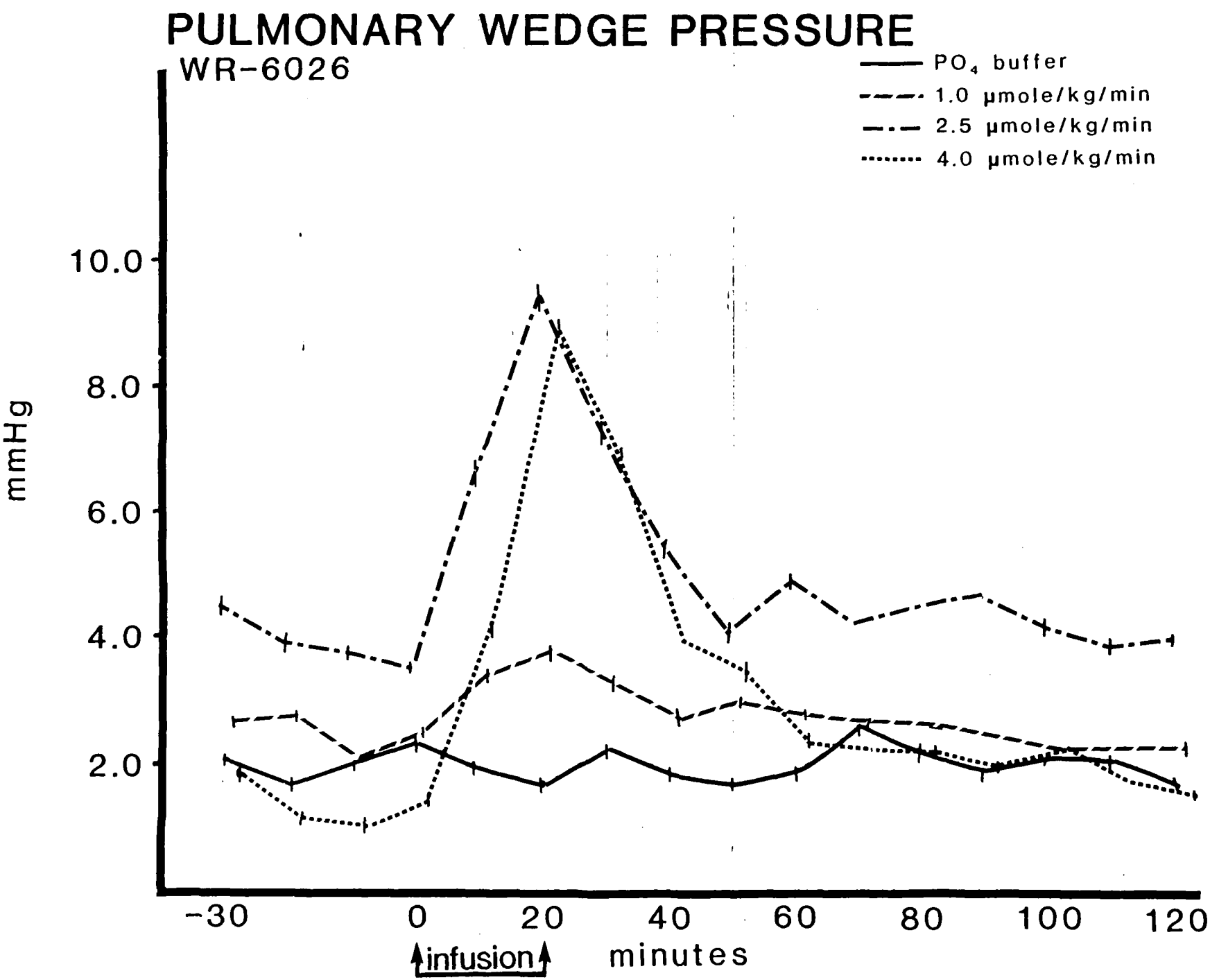

PULMONARY WEDGE PRESSURE
WR-6026
PO4 buffer
1.0 µmole/kg/min
2.5 µmole/kg/min
4.0 µmole/kg/min
mmHg
10.0
8.0
6.0
4.0
2.0
-30
0
20
40
60
80
100
120
infusion
minutes

figure 20B

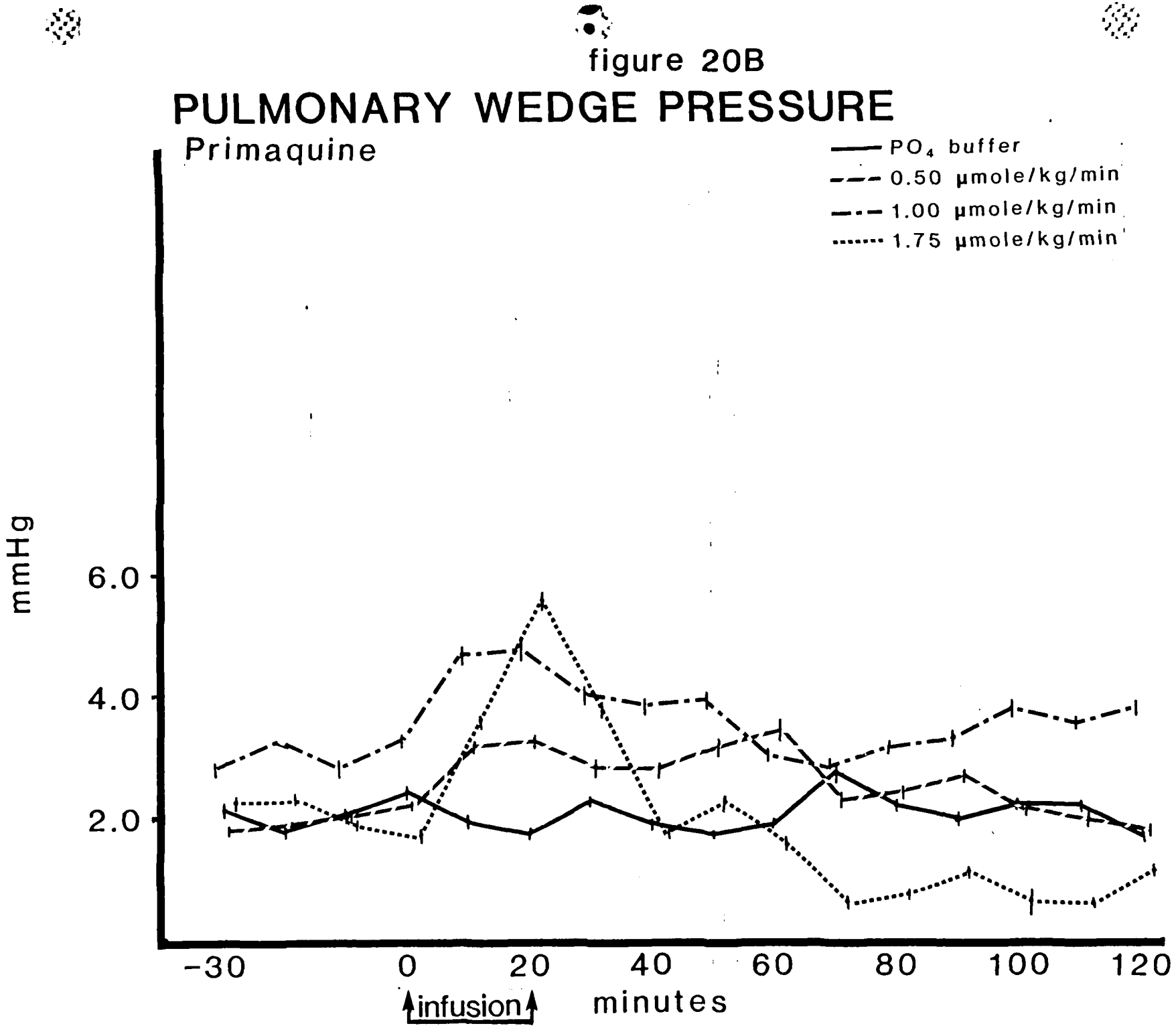
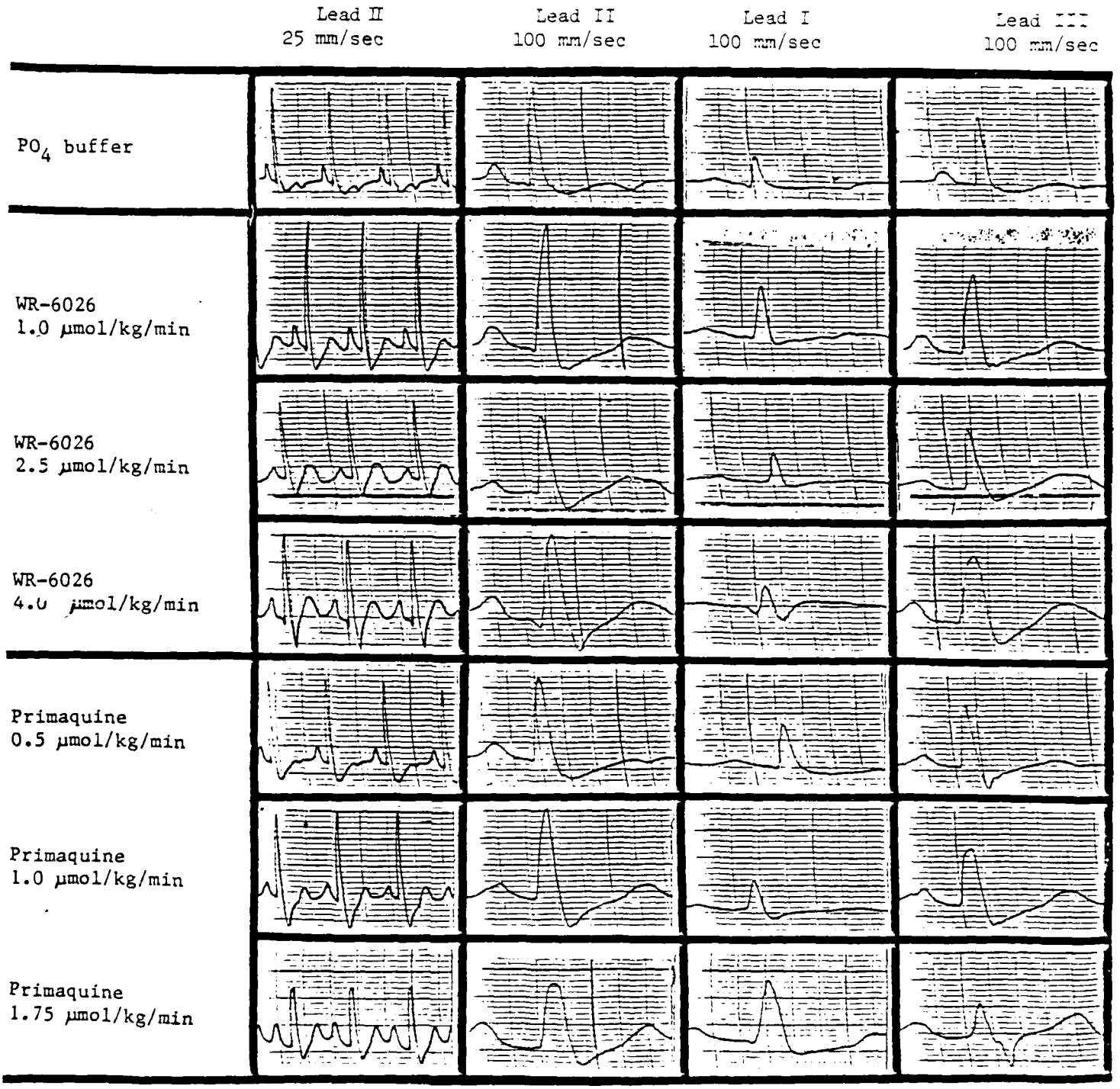

PULMONARY WEDGE PRESSURE
Primaquine
PO4 buffer
0.50 µmole/kg/min
1.00 µmole/kg/min
1.75 µmole/kg/min
mmHg
6.0
4.0
2.0
-30
0
20
40
60
80
100
120
infusion
minutes

Fig. 21

Representative EKG tracings
at +20 minutes

1 mv = 1 cm



APPENDIX E

Variable Recordings

[redacted]

Tracing 1A
Time = 0

Heart Rate beats/min Time = 0
WR-6026 @ 6.0 μmole/kg/min. to 20 min.

11/11/62

160

80

25mm/min EKG lead II 25mm/sec

II

Tidal Volume ml/breath

200

0

Arterial Blood Pressure mm Hg

100

0

Intrapleural pressure

Pulmonary Artery Pressure mm Hg

20

0

20

Compliance cc

0

Resistance cm

0

[redacted]

Tracing 1 B

Time = +10

Heart Rate

Time = +10
W2-6036 @ 60 μmac/kg/min for 20 min.
11/4/82

-160

-80

EKG Lead I

25 mm/mV | 25 mm/sec

Tidal Volume
ml/breath

-200

-0

Arterial Blood Pressure
mm Hg

-100

+10

-0

Intrapleural Pressure

Pulmonary Artery Pressure
mm Hg

-20

-0

-20

Compliance
CL

-0

Resistance
RL

-5

-0

Heart rate
beats/min.

Time = +20 min
WR: 6046 @ 6.0 grams/kg/min for 20 min.
4/11/82

Tracing 1 C
Time = +20

-160

-80

EKG lead II

25 mm/min

25 mm/sec

Tidal volume
ml/breath

-200

-0

Arterial Blood Pressure
mm Hg

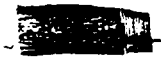
-100

-0

Intrapleural pressure

Pulmonary Artery Pressure
mm Hg

-20



-0

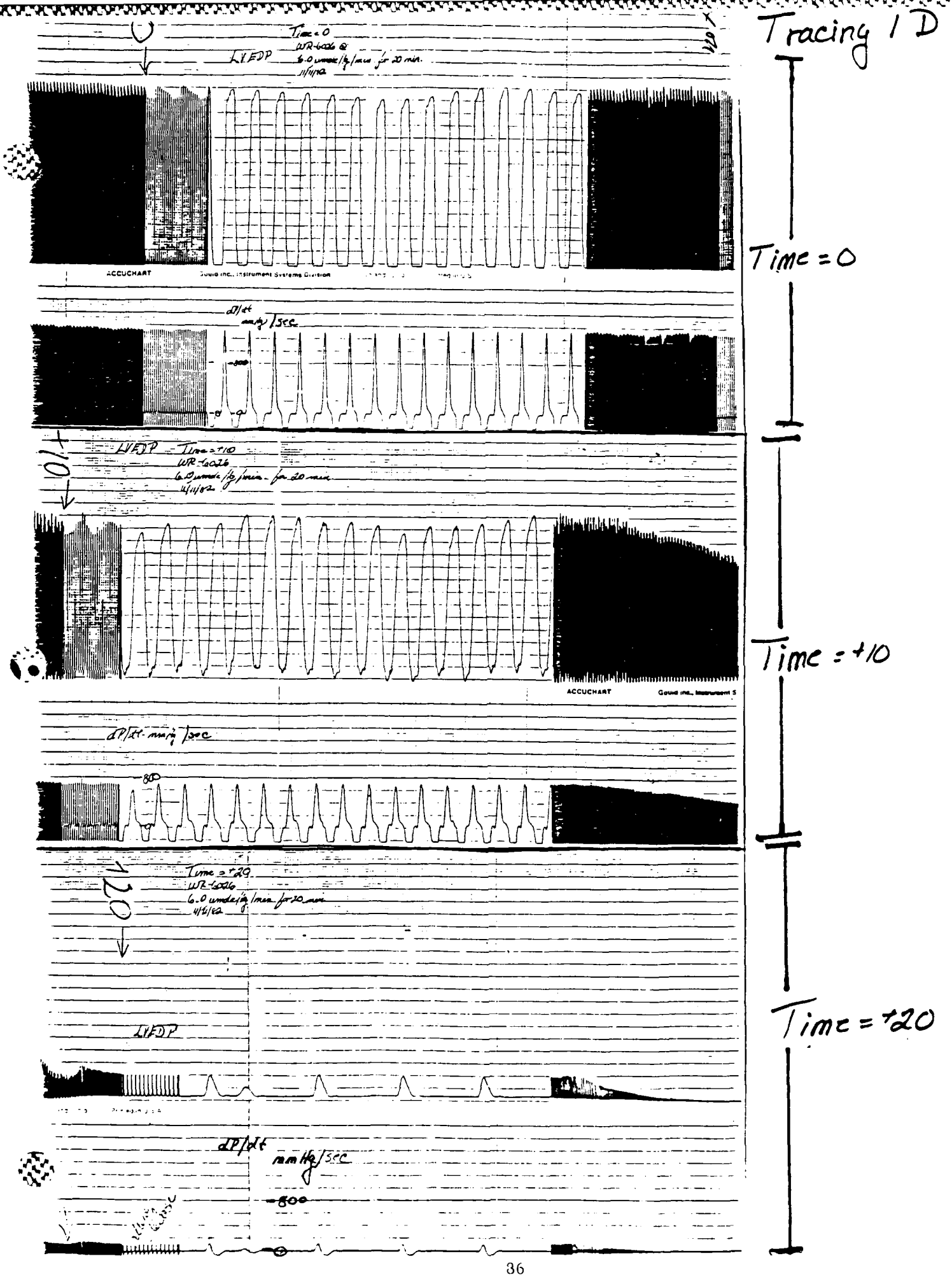
-20

Compliance
cu

-10

Resistance
ru

-5


Tracing 1 D
Time = 0
Time = +10
Time = +20
LVEDP
ACCUCHART
dP/dt
mmHg/sec
-800
+10
+20

[redacted]

Heart Rate
beats/min

Time = 0
Primaquine
2.0 micro/kg/min for 20 min
2/23/83

Tracing 2 A
Time = 0

-160

-80

EKG Lead II
25 mm/min
25 mm/sec

Tidal Volume
ml/breath

-200

-0

Intrapleural Pressure

MAP mmHg

-100

-0

Pulmonary Artery Pressure mmHg

-20

-0

[redacted]

Tracing 2B

Time = +10

Heart Rate
beats/min

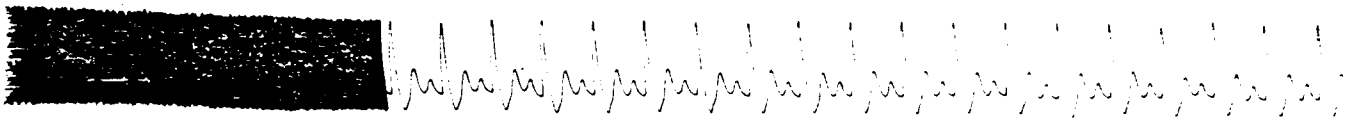
Time = +10
Primaquine
20 units/kg/day for 20 mos
2/23/83

-160

-50

EKG lead II

25 mm/min | 25 mm/sec



Tidal Volume
ml/breath

-200

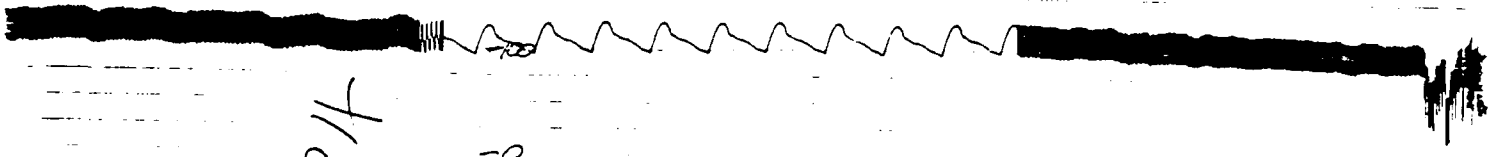
-0

Intrapleural Pressure

ABP
mm Hg

-100

-0

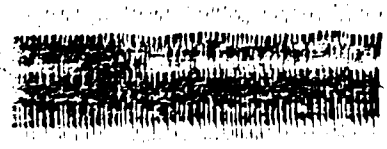


O/K

Pulmonary Artery Pressure mm Hg

-20

-0



ing 2D

Tracing 2C

Heart Rate (not triggering due to arrhythmias) -160

Time = +20

Time = +20

-80

= 0

EKG Lead II

25mm/sec

Volume rate

200

-0

Intrapleural pressure

= +10

ABP

-100

-0

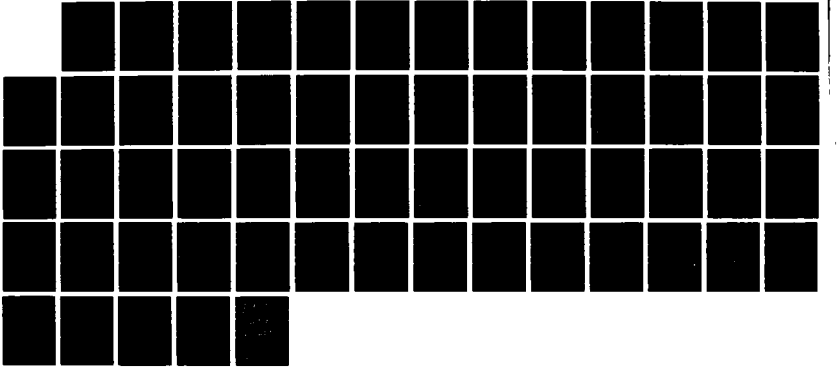
ne = +20

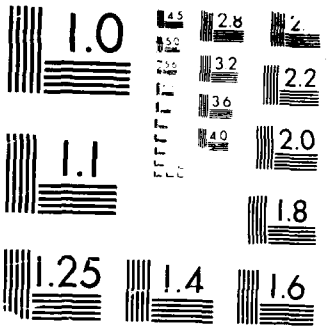
Pulmonary Artery Pressure mmHg

-20

AD-A194 390 STUDY OF THE EFFECTS OF DRUGS UPON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS(U) TENNESSEE UNIV CENTER FOR THE HEALTH SCIENCES MEMPHIS R W CALDWELL ET AL. 2/2

UNCLASSIFIED 01 FEB 85 DAMD17-83-C-3011 F/G 6/15 NL





MICROCOPY RESOLUTION TEST CHART

APPENDIX F

Tabulated Data

Note: (1) Numerical entries under time represents minutes

(2) For definitions of column heading abbreviations see Appendix A

DK. Q-buffer WT 1091kg

DOSE 4 ml/min for 60 min DATE 12/6/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	480	4.0	1.92	5.0	20	100/[illegible]	144	1.67	3600	5.0	27.5	16.47	50.6	51.2	7.258	38.9	53.0	7.247	37.2
-20	510	4.0	2.04	5.0	20	[illegible]	142	1.56	3500	4.0	24.0	15.38							
-10	490	4.0	1.96	5.0	20	[illegible]	140	1.51	3400	4.0	21.0	13.91							
0	460	4.0	1.84	5.0	20	[illegible]	138	1.50	3200	5.0	22.5	13.67	67.2	48.7	7.252	51.1	55.8	7.216	37.0
10	440	5.0	2.20	5.0	20	[illegible]	130	1.42	3200	5.0	14.0	9.40							
20	420	5.5	2.31	5.0	20	[illegible]	134	1.66	3000	5.5	11.5	6.93	69.0	42.5	7.293	51.6	49.1	7.262	38.0
30	450	5.0	2.25	5.0	20	[illegible]	127	1.61	3300	4.0	9.5	5.90							
40	430	5.5	2.37	5.0	20	[illegible]	132	1.54	3100	4.0	9.0	5.84	70.6	45.1	7.221	49.0	47.8	7.272	38.7
50	410	5.5	2.26	5.0	20	[illegible]	126	1.62	3200	4.0	9.0	5.56							
60	480	6.0	2.88	5.0	20	[illegible]	128	1.61	4000	4.5	7.0	4.97	71.1	36.0	7.347	42.8	45.3	7.299	40.5
70	510	9.0	4.59	5.0	20	[illegible]	124	1.61	4400	4.5	9.0	5.59							
80	490	7.5	3.68	5.0	6.5	[illegible]	120	1.61	3800	3.5	16.0	11.11	51.6	43.0	7.326	39.2	47.8	7.290	41.5
90	470	5.0	2.35	5.0	6.5	[illegible]	120	1.57	3300	4.0	18.0	12.17							
100	500	5.0	2.50	5.0	6.5	[illegible]	116	1.74	3300	5.0	17.0	11.91	50.7	41.9	7.356	36.8	47.1	7.263	40.3
110	490	5.0	2.45	5.0	6.5	[illegible]	114	1.74	3600	5.0	17.5	16.22							
120	480	5.5	2.64	5.0	6.5	[illegible]	[illegible]	1.74	3200	4.0	17.5	15.50	59.2	43.8	7.271	37.4	41.3	7.361	39.2

DRUG PO2 buffer WT 9.09kg

DOSE 4ml/min for 20min DATE 10/18/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30																			
-20																			
-10																			
0																			
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

DRUG PO$_4$-buffer WT 10.91 kg
DOSE [illegible] DATE 7/16/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	$\overline{PAP}$	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	[illegible]	16.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.40	[illegible]	0.0	7.0	5.00	[illegible]	38.8	[illegible]	[illegible]	44.0	7.375	35.7
-20	[illegible]	17.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.34	800	-0.5	7.0	[illegible]							
-10	[illegible]	18.0	[illegible]	14.9	[illegible]	[illegible]	[illegible]	1.24	[illegible]	-1.0	6.5	5.24							
0	140	[illegible]	[illegible]	14.0	[illegible]	[illegible]	164	1.24	[illegible]	-1.0	6.0	4.84	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.412	25.0
10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		168	1.14	[illegible]	-1.0	6.0	5.26							
20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	* -	6.0	6.00	88.0	[illegible]	[illegible]	49.7	[illegible]	7.352	24.8
30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	-	[illegible]	[illegible]							
40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	-	7.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	-	8.0	[illegible]							
60	[illegible]	[illegible]	[illegible]	15.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	-	8.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	34.8	[illegible]	[illegible]
70	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	136	[illegible]	[illegible]	-	7.0	[illegible]							
80	[illegible]	[illegible]	[illegible]	16.0	[illegible]	[illegible]	[illegible]	[illegible]	160	-	6.0	4.84	[illegible]	[illegible]	[illegible]	46.1	33.0	[illegible]	[illegible]
90	[illegible]	44.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.07	[illegible]	-	5.5	5.14							
100	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.06	[illegible]	-	5.5	[illegible]	[illegible]	[illegible]	[illegible]	45.0	33.9	[illegible]	[illegible]
110	[illegible]	[illegible]	4.65	[illegible]	[illegible]		[illegible]	1.11	140	-	5.5	[illegible]							
120	[illegible]	[illegible]	[illegible]	[illegible]	0		[illegible]	1.06	160	-	5.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* [illegible]

DRUG Ph-buffer WT 12.27kg

DOSE ~~1ml/min for 30 min~~ DATE 6/30/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A Po_2	A Pco_2	A pH	V Po_2	V Pco_2	V pH	Hct
-30	4.0	3.5	1.88	74	47.0	[illegible]	152	2.01	880	1.5	12.5	6.25	66.6	41.4	7.390	41.0	46.6	7.283	39.7
-20	4.0	3.5	0.00	0	0.0	110/60	0.0	0.00	860	1.5	12.5	5.58							
-10	4.0	2.5	1.18	50.0	45.0	110/60	151	1.40	840	1.5	11.0	7.86							
0	4.0	3.0	1.44	48.0	48.0	110/60	140	1.92	900	2.0	11.0	8.33	65.8	45.0	7.265	46.5	49.1	7.245	41.0
10	3.0	3.0	1.41	54.0	50.0	110/60	130	1.62	940	2.0	10.5	8.50							
20	3.0	4.0	1.44	36.0	51.0	110/60	124	1.61	980	1.5	9.0	9.00	76.3	45.4	7.315	42.5	42.5	7.380	42.3
30	[illegible]	5.5	1.62	[illegible]	[illegible]	[illegible]	130	1.67	940	0.5	7.5	7.07							
40	[illegible]	7.5	[illegible]	[illegible]	[illegible]	[illegible]	134	1.68	940	0.5	7.0	6.48	91.4	43.6	7.355	47.9	41.5	7.[illegible]	40.7
50	[illegible]	9.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.5	7.5	6.25							
60	3.40	10.5	[illegible]	40.0	47.0	110/60	139	1.54	880	0.5	8.0	5.19	95.3	[illegible]	7.364	40.6	38.9	7.385	40.8
70	3.40	9.5	[illegible]	42.0	47.0	110/60	164	1.68	900	0.5	8.0	4.76							
80	3.60	9.0	[illegible]	40.0	45.0	110/60	164	1.62	840	0.0	7.5	4.63	95.1	37.1	7.383	42.5	36.9	7.367	41.2
90	3.50	9.5	[illegible]	60.0	[illegible]	110/60	167	1.58	840	0.0	7.0	5.47							
100	3.40	8.5	[illegible]	60.0	[illegible]	110/60	160	1.20	640	0.0	6.5	5.42	89.3	[illegible]	7.333	44.9	35.8	7.341	48.8
110	3.40	7.5	[illegible]	60.0	48.0	110/60	156	1.52	640	0.0	6.5	5.23							
120	3.40	[illegible]	[illegible]	52.0	46.0	[illegible]	142	1.36	580	0.0	6.0	6.25	92.1	[illegible]	7.363	[illegible]	34.1	7.321	45.0

DRUG PO4-buffer WT 10.15kg

DOSE ~~1ml/min for 2min~~ DATE 6/28/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30		6.0					122	1.44	120	2.5	14.0	9.72	76.5	34.8		45.4	37.9	7.306	42.8
-20		6.0			6.0		122	1.52	140	2.5	15.0	9.87							
-10					6.2		120	1.50	130	3.0	15.0	10.00							
0		6.0					120	1.41	130	3.5	15.0	10.64	80.7	33.1	7.371	47.6	37.2	7.342	43.7
10		7.0					118	1.52	120	2.5	12.5	8.22							
20		7.0					120	1.31	140	3.5	11.5	8.58	85.9	31.0	7.362	45.4	36.1	7.355	43.7
30							121	1.22	140	1.0	11.0	7.02							
40								1.27		2.5	11.0	8.66							46.0
50								1.22		0.0	6.0	7.84							
60								1.27		3.5	12.0	9.45	91.1						47.0
70									160	-1.0	12.0	9.87							
80										1.0	11.0	9.73	94.4	34.7	7.413	49.1		7.371	
90								1.01		0.5	10.0	9.90							
100					10		120	1.02	120	2.0	10.0	9.45				49.0	39.8	7.359	41.7
110		10.5						2.96		2.5	10.0	10.42							
120		11.0						1.08		1.0	12.0	7.96				41.4			45.5

DRUG SR-6026 WT 12.04 kg

DOSE 10 μmole/kg/min DATE 1/6/84

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	220	20	2.6	42	-	[illegible]	176	4.36	[illegible]	5.0	18/5	10.20	39.1	51.7	1.210	32.4	55.6	1.217	45.3
-20	215	25	[illegible]	[illegible]	-	[illegible]	[illegible]	[illegible]	[illegible]	5.0	16/5	8.25							
-10	225	20	[illegible]	37	-	[illegible]	168	[illegible]	[illegible]	5.0	15/0	7.21							
0	230	25	[illegible]	39.0	-	[illegible]	168	12.6	[illegible]	5.5	16/0	6.25	71.8	[illegible]	1.165	45.1	50.7	1.236	41.0
10	270	30.0	5.4	42.0	-	[illegible]	172	13.2	[illegible]	6.0	18/0	3.55							
20	255	26.0	3.32	39.0	-	[illegible]	172	13.3	[illegible]	6.0	16/0	5.02	63.2	42.8	1.269	48.5	44.2	1.283	40.7
30	230	40	[illegible]	[illegible]	-	[illegible]	170	13.8	[illegible]	7.0	13/0	5.64							
40	225	40	[illegible]	[illegible]	-	[illegible]	[illegible]	[illegible]	[illegible]	5.0	14/0	5.81	57.8	41.1	[illegible]	43.0	41.9	1.243	45.7
50	[illegible]	50	[illegible]	[illegible]	-	[illegible]	[illegible]	[illegible]	[illegible]	4.0	13/0	6.57							
60	230	30	[illegible]	37.0	-	[illegible]	170	[illegible]	[illegible]	4.0	15/0	8.00	35.1	[illegible]	[illegible]	[illegible]	48.9	1.264	46.8
70	[illegible]	[illegible]	[illegible]	[illegible]	-	[illegible]	0	[illegible]	[illegible]	5.0	16/5	8.53							
80	230	30	[illegible]	[illegible]	-	[illegible]	184	[illegible]	[illegible]	5.5	12/0	9.27	45.4	[illegible]	1.116	[illegible]	61.0	1.174	50.0
90	[illegible]	[illegible]	[illegible]	[illegible]	-	[illegible]	188	15.2	[illegible]	5.5	12/0	8.00							
100	[illegible]	35	[illegible]	32.2	-	[illegible]	176	15.0	[illegible]	5.0	11/0	7.33	48.4	[illegible]	1.162	37.0	65.6	1.144	48.3
110	260	25	1.62	30	-	[illegible]	172	[illegible]	[illegible]	5.5	11/0	8.53							
120	[illegible]	30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	5.0	20	6.06	44.7	[illegible]	1.172	[illegible]	61.7	1.155	45.0

DRUG WR-6026 WT 8.52 kg

DOSE ~~4 gm/kg/air~~ DATE 11/18/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	2.0	4.5	1.17	2.0	1.2	[illegible]	156	1.58	2000	3.0	11.5	7.28	71.1	40.5	7.310	42.2	44.6	7.295	37.5
-20	2.0	4.5	1.12	2.0	2.0	[illegible]	154	1.60	2100	3.0	8.0	5.00							
-10	2.0	4.5	1.08	2.0	2.0	[illegible]	152	1.54	3100	3.0	11.0	7.14							
0	2.0	4.5	1.08	2.0	4.0	[illegible]	140	1.36	2050	3.0	11.0	7.05	77.1	36.5	7.345	51.7	45.6	7.300	40.5
10	2.5	5.0	1.22	2.0	1	[illegible]	136	1.28	2600	5.0	15.0	9.49							
20	2.0	6.5	1.09	2.0	[illegible]	[illegible]	134	1.60	3110	5.0	13.0	8.12	90.8	34.2	7.368	45.1	44.3	7.311	38.0
30	1.40	7.5	1.08	2.0	5	[illegible]	132	1.64	2250	4.0	9.0	5.84							
40	1.50	8.5	1.07	2.0	2.0	[illegible]	130	1.58	2350	4.5	9.0	5.66	72.1	40.9	7.313	51.1	45.1	7.295	40.7
50	1.50	10.0	1.40	2.0	[illegible]	[illegible]	[illegible]	1.60	2200	4.0	9.0	5.00							
60	1.50	8.5	1.0	2.0	[illegible]	[illegible]	[illegible]	[illegible]	2300	4.0	9.2	5.56	70.1	42.2	7.29	53.0	47.4	7.274	41.0
70	1.50	9.5	1.40	2.0	5	[illegible]	[illegible]	[illegible]	2300	4.0	9.0	5.84							
80	1.50	10.0	1.50	2.0	3.0	[illegible]	[illegible]	[illegible]	2300	4.0	10	6.48	64.1	42	7.355	47.2	48.6	7.286	42.5
90	1.50	9.5	1.47	2.0	[illegible]	[illegible]	[illegible]	1.64	2400	5.5	10	5.64							
100	1.45	8.5	1.53	2.0	[illegible]	[illegible]	[illegible]	1.68	1700	3.0	7.0	6.20	64.3	42.1	7.282	38.9	53.6	7.249	41.0
110	1.50	8.5	1.42	2.0	[illegible]	[illegible]	[illegible]	1.60	2.10	4.0	6.5	6.03							
120	1.50	8.5	1.4	2.0	2.0	[illegible]	[illegible]	1.64	1900	5.0	8.0	6.65	62.1	42.4	7.317	35.3	53.5	7.255	39.7

DRUG WR-6026 WT 109 kg

DOSE 1 μmole/kg/min DATE 10/27/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A Po_2	A Pco_2	A pH	V Po_2	V Pco_2	V pH	HCT
-30	120	10.0	1.20	18.0	4.3	114/65	140	2.00	4100	1.0	6.5	3.25	51.3	61.8	7.120	18.3	66.8	7.128	42.8
-20	180	9.5	1.71	18.0	5.2	122/75	148	1.81	4100	1.0	5.5	3.04							
-10	220	8.5	1.87	18.0	5.1	120/80	140	1.93	4300	1.0	5.5	2.85							
0	220	8.0	1.76	18.0	5.0	124/90	130	2.08	4400	1.0	6.0	2.88	31.9	76.5	7.045	16.1	76.8	7.061	43.3
10	220	11.5	2.61	18.0	5.1	120/80	142	2.27	4750	1.0	6.0	2.64							
20	230	12.5	2.72	18.0	5.2	120/80	134	2.37	4800	1.0	5.0	2.11	41.6	71.0	7.069	23.3	79.9	7.042	43.0
30	220	11.0	2.45	18.0	5.0	120/85	130	1.94	4850	1.0	5.0	2.52							
40	230	11.5	2.59	18.0	5.0	120/80	132	1.84	4850	1.0	5.5	2.99	52.9	61.2	7.090	36.8	82.3	7.048	42.5
50	230	10.0	2.30	18.0	5.0	120/80	128	1.78	4750	1.0	5.5	3.30							
60	230	10.2	2.34	17.5	5.1	120/80	126	1.66	4750	1.0	5.0	3.01	52.5	63.0	7.117	41.3	16.5	7.059	41.2
70	220	10.0	2.20	16.0	5.5	120/80	126	1.66	4700	1.0	5.0	3.01							
80	230	10.0	2.30	16.0	5.8	120/80	120	1.60	4850	0.5	6.0	3.75	50.6	65.6	7.121	41.3	75.8	7.083	40.5
90	220	10.0	2.20	16.0	5.5	120/80	122	1.58	4850	0.0	6.0	3.80							
100	220	10.0	2.20	16.0	5.8	120/80	122	1.64	4700	0.0	6.0	3.66	62.2	52.4	7.161	42.9	74.1	7.044	40.0
110	220	10.5	2.31	16.0	6.0	120/80	120	1.62	4825	0.0	6.0	3.75							
120	220	12.0	2.64	16.0	5.5	120/80	120	1.76	4900	0.0	6.5	4.17	62.1	52.5	7.179	24.4	68.8	7.124	37.2

DRUG WR 6026 WT 8.18 kg

DOSE 6 Quinuclidinyl DATE 4/8/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30																			
-20																			
-10																			
0																			
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

DRUG WR-6026 WT 9.77kg

DOSE 1.0 μmole/kg/min DATE 8/30/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30												6.65	58.9	45.4					44.3
-20										5.0	13.0	7.30							
-10										4.5	12.0								
0				0						5.0	12.0		21.6	47.8		43.3		7.193	46.2
10										5.0	11.0	6.40							
20										6.0	11.0	7.05	61.0	43.7		46.1		7.239	42.7
30											9.5	5.97							
40				0							8.0		87.4	51.8					
50																			
60				0							7.5		73.2						
70				0						3.0	8.0								
80													64.0						
90										4.0	10	6.48							
100				1						4.0	9.5		63.9						
110				5						4.0	9.0	7.50							
120										4.0	9.2		58.4						

DRUG WR-6026 WT 13.64kg

DOSE 4 μg/kg/min DATE 8/16/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30																			
-20																			
-10																			
0																			
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

DRUG WR-6026 WT 12.84 kg

DOSE 25 μmole/kg/min DATE 4/9/84

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	375	50	18.8	2.01	-	[illegible]	150	18.0	[illegible]	6.0	18.5	10.28	59.2	42.8	7.41	42.6	49.7	7.264	50.3
-20	350	55	19.1	2.13	-	[illegible]	150	18.0	2.22	6.0	18.5	10.28							
-10	375	50	18.7	2.15	-	[illegible]	140	18.0	2.22	5.0	17.0	9.44							
0	375	60	22.5	2.21	-	[illegible]	150	17.3	2.00	5.0	16.5	9.52	69.2	37.4	7.436	47.3	47.3	7.297	51.7
10	375	75	28.13	2.25	-	[illegible]	170	15.6	1.375	11.0	19.0	6.18							
20	375	62.5	23.4	2.08	-	[illegible]	150	15.0	1.20	6.5	20.0	16.22	78.0	28.6	7.489	33.4	34.2	7.347	53.0
30	375	75.5	28.3	2.13	-	[illegible]	150	16.2	1.25	10.5	16.0	8.10							
40	350	70.0	24.8	2.11	-	[illegible]	150	15.3	1.10	9.0	17.0	10.51	71.5	[illegible]	7.418	30.1	38.7	7.404	52.7
50	375	76.5	28.8	2.0		[illegible]	[illegible]	17.2	1.30	9.0	18.2	7.05							
60	425	77.0	32.7	2.4		[illegible]	150	16.6	1.30	9.0	21.5	10.27	69.5	28.9	7.514	33.2	37.8	7.363	52.0
70	410	75.5	30.8	2.1	-	[illegible]	170	17.2	1.30	8.0	16.0	10.55							
80	425	69.2	29.3	1.92	-	[illegible]	160	15.3	1.30	7.5	17.0	9.77	68.1	29.9	7.394	32.0	38.7	7.341	55.3
90	375	71.5	26.8	2.53		[illegible]	160	17.2	1.450	7.0	16.5	9.12							
100	330	67.5	22.3	1.85		[illegible]	140	15.8	1.20	6.0	17.5	11.22	69.1	29.5	7.389	28.1	34.4	7.342	53.7
110	310	69.0	21.4	1.86		[illegible]	135	14.5	1.00	7.0	17.0	10.78							
120	320	69.5	22.2	2.01	-	[illegible]	140	14.4	1.00	7.0	17.0	10.64	[illegible]	32.2	7.397	28.3	34.8	7.327	[illegible]

DRUG WR-6026 VVI 10.0 kg

DOSE ~~2.5 mcg/kg/min~~ DATE 12/8/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	390	9.0	3.42	340	6.2	100/70	160	1.82	4400	5.0	16.0	8.79	77.8	40.8	7.397	49.0	44.8	7.289	32.7
-20	380	10.0	3.80	340	5.0	100/65	160	1.81	4500	4.5	15.0	8.29							
-10	380	9.5	3.53	346	5.0	100/70	160	2.09	4300	5.0	22.0	10.53							
0	410	7.0	2.87	300	6.0	100/60	170	1.83	4400	5.0	20.0	10.93	75.1	42.2	7.387	44.5	45.8	7.262	33.2
10	385	13.0	4.97	180	5.0	110/105	135	1.80	4950	7.0	16.5	9.17							
20	390	25.0	5.00	160	1.0	110/65	130	1.58	2050	11.0	17.5	11.08	85.2	37.2	7.325	47.4	44.0	7.275	33.0
30	340	22.0	5.48	180	0.5	110/70	120	1.58	2700	9.0	13.5	8.54							
40	340	26.5	5.10	180	1.0	110/70	120	1.71	2400	7.0	13.5	7.89	86.1	35.6	7.388	42.6	46.1	7.285	33.7
50	330	23.0	5.70	220	1.0	110/70	120	1.60	2200	6.5	13.0	8.12							
60	330	26.0	5.80	216	1.0	110/70	120	1.52	1700	6.0	13.0	8.55	82.9	34.0	7.342	40.5	40.8	7.303	37.0
70	320	34.5	7.22	210	0.5	110/70	120	2.05	1850	7.0	12.0	11.43							
80	300	34.5	6.90	200	0.5	110/70	120	1.91	1850	7.0	11.5	11.06	82.8	34.6	7.37	38.5	44.9	7.271	38.5
90	280	35.0	6.90	200	1.0	110/70	120	1.70	1900	7.5	13.5	14.85							
100	290	36.0	6.90	200	0.5	110/70	120	1.91	2000	6.0	12.0	11.88	81.4	36.9	7.317	31.2	46.5	7.258	36.5
110	270	34.0	6.91	200	1.0	110/70	120	1.82	2150	5.0	13.0	12.74							
120	270	29.5	5.78	200	1.0	110/70	120	0.96	1400	4.0	6.25	13.02	86.2	34.0	7.338	35.6	46.6	7.273	35.0

DRUG WR 6026 VV 9.32kg

DOSE ~~2.5 μmole/kg/min~~ DATE 11/22/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	400	3.0	1.20	17.0	7.1	[illegible]	140	1.62	1300	1.0	16.0	9.88	60.3	52.1	1.359	43.3	56.6	7.262	43.3
-20	400	4.5	1.80	15.5	7.0	170/60	144	1.46	1300	4.5	650.0	13.70							
-10	450	3.0	1.35	15.5	7.5	160/65	148	1.32	1450	4.5	17.0	12.88							
0	400	4.5	1.80	15.0	7.5	155/65	136	1.26	1800	4.5	14.5	12.08	58.7	55.8	7.203	39.1	62.9	7.190	44.8
10	450	6.0	2.70	15.5	4.5	150/70	140	1.66	1500	6.0	15.0	9.04							
20	450	9.5	4.28	15.0	7.0	150/70	140	1.71	1800	7.0	15.0	8.77	91.6	43.2	7.286	57.8	48.5	7.266	45.0
30	450	7.0	3.15	15.0	7.8	150/70	140	1.67	1825	6.0	13.5	8.23							
40	400	4.5	1.80	15.5	7.1	150/70	140	1.62	1600	5.5	12.0	7.42	78.5	46.8	7.260	53.7	51.5	7.249	45.0
50	450	4.5	1.71	15.0	7.8	150/70	140	1.57	1600	6.0	13.0	8.28							
60	450	5.5	2.48	15.2	7.8	150/70	140	1.59	1800	5.5	12.5	7.92	65.5	52.0	7.[illegible]	46.5	57.4	7.238	46.0
70	450	4.0	1.80	15.0	7.1	150/70	140	1.61	2000	5.0	13.0	10.83							
80	450	4.0	1.80	15.0	7.1	150/70	140	1.61	1550	4.0	12.0	9.38	66.8	54.1	7.[illegible]	44.2	61.2	7.211	48.2
90	450	4.5	2.03	15.5	7.6	150/70	140	1.71	1700	3.5	11.0	8.73							
100	450	4.7	2.12	15.5	7.8	150/70	140	1.71	1500	3.5	11.5	10.08	71.8	57.6	7.241	45.8	60.7	7.245	47.8
110	450	4.1	1.85	15.5	7.5	150/70	140	1.04	1550	4.0	12.0	11.54							
120	450	4.2	1.89	15.0	7.5	150/70	140	1.05	1570	4.5	10.0	9.80	81.[illegible]	48.0	7.260	40.1	66.6	7.213	47.0

DRUG WR-6026 WT 10.23 kg

DOSE ~~25 μmol/kg/min~~ DATE 10/19/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30										0.0			-	-	-	-	-	-	-
-20										1.0		5.53							
-10										1.0	10.5								
0										1.0		6.00							
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

SVR dyn sec/cm⁵

DRUG WR-6026 WT 9.77kg

DOSE ~~2.5 mmole/kg/min~~ DATE 10/14/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30											8.0	5.19	100.5			38.6	46.5	7.312	
-20								1.45			9.0	6.29							
-10											7.5	4.60							
0											7.0	4.67	101.9			44.4	51.8	7.191	
10									1800	6.0	12.0	7.95							
20											11.0	7.91							
30											7.0	5.03							
40								1.34		1.5	5.5	4.10							
50										1.0	4.5	3.63							
60											5.5	4.23							
70										1.5	4.5	4.22							
80										1.0	4.0	3.77							
90										0.5	3.5	3.30							
100										1.0	4.0	3.92							
110											3.5	3.64							
120											3.5	3.34							

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DRUG WR-6026 WT 12.73 kg

DOSE ~~25 μmol/kg/min~~ DATE 8/11/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30																			
-20																			
-10																			
0																			
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

LOT

DRUG [illegible] WT 12.04 kg

DOSE [illegible] DATE 11/9/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	P_{O_2} A	P_{CO_2} A	PH A	P_{O_2} V	P_{CO_2} V	PH V	HCT
-30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	204?	2.57	2600	[illegible]	18.0?	[illegible]	55.0	49.1	7.254?	44.8	50.2	7.279	37.0
-20	[illegible]	7.0?	[illegible]	[illegible]		[illegible]	184	2.53	2450	[illegible]	17.0	[illegible]							
-10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.50	2400	[illegible]	[illegible]	[illegible]							
0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.51	2400	[illegible]	[illegible]	[illegible]	66.1	47.5	7.278	47.7	53.2	7.260	39.2
10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.21	2100	[illegible]	[illegible]	[illegible]							
20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.28	[illegible]	[illegible]	[illegible]	[illegible]	77.3	42.2	7.312	49.8	50.6	7.298	37.5
30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.22?	[illegible]	[illegible]	[illegible]	[illegible]							
40	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	73.0	45.3	7.291	47.7	51.6	7.265	38.5
50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]							
60	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	77.7	44.1	7.310	47.7	50.8	7.278	39.8
70	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.84	1500?	[illegible]	[illegible]	[illegible]							
80	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	1.81	[illegible]	[illegible]	[illegible]		78.7	40.3	7.345	42.9	49.7	7.292	40.7
90	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.67	[illegible]	[illegible]	[illegible]								
100	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.60	[illegible]	[illegible]	[illegible]		73.1	42.0	[illegible]	[illegible]	48.7	7.295	40.0
110	[illegible]	8.0?	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.58	[illegible]	[illegible]	[illegible]								
120	[illegible]	8.0?	[illegible]	[illegible]	[illegible]	[illegible]		1.56	[illegible]	[illegible]	[illegible]		60.8	48.1	[illegible]	41.6	[illegible]	7.266	40.0

DRUG UR-6026 WT 8.52 kg

DOSE 10 mcg/kg/min DATE 12/16/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	280	4.5	1.26	28.5	6.8	130/85	156	1.71	3500	3.0	250	14.62	55.7	48.4	7.259	36.7	52.5	7.244	38.2
-20	305	4.5	1.37	27.5	8.0	125/80	156	1.70	3400	2.5	210	12.35							
-10	295	4.0	1.22	25.0	9.0	127/85	140	1.66	3100	3.5	19.5	11.75							
0	300	4.5	1.35	25.0	9.0	120/80	140	1.52	3100	1.5	17.0	11.18	67.3	46.3	7.281	37.7	51.0	7.242	40.7
10	160	21.5	2.58	19.0	1.5	140/105	160	1.80	2400	5.5	14.5	8.06							
20	135	27.5	3.44	13.5	1.5	135/75	130	1.28	1300	10.0	30.0	15.62	75.5	38.8	7.294	45.8	43.9	7.261	43.5
30	125	31.5	3.91	14.5	2.0	135/100	120	1.40	1700	5.5	15.5	11.07							
40	120	31.0	3.72	15.0	2.0	135/105	119	1.38	1900	6.0	16.0	11.59	69.8	42.5	7.266	47.8	48.8	7.253	46.7
50	120	28.5	3.42	16.0	2.0	130/100	120	1.35	1900	6.0	17.0	12.59							
60	130	30.5	3.66	18.0	1.5	130/100	128	1.32	1950	5.0	14.5	10.98	72.9	45.3	7.264	45.1	50.2	7.238	48.0
70	135	27.0	3.38	18.0	1.5	130/95	127	1.16	2000	2.5	11.0	9.48							
80	135	23.0	2.88	17.0	2.0	130/95	130	1.08	1900	3.5	11.0	10.18	71.1	43.2	7.280	41.4	53.4	7.245	49.3
90	135	27.5	3.16	15.5	2.0	130/95	128	0.98	1800	4.0	12.0	12.24							
100	140	29.0	3.19	16.0	0.8	135/105	130	0.99	1800	4.0	12.0	12.12	73.4	41.1	7.285	36.8	53.9	7.240	50.5
110	115	28.0	3.22	14.0	0.7	135/100	120	0.90	1800	4.0	11.0	12.22							
120	115	26.5	3.05	13.0	1.0	135/105	110	0.82	1900	4.5	11.5	14.02	75.2	41.4	7.277	33.3	52.6	7.244	50.0

DRUG WR-6026 WT 12.01kg

DOSE 40 μmole/kg/min DATE 12/7/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	420	6.5	5.73	14.0	6.0	175/110	130	2.06	2000	5.5	25.0	12.14	50.6	48.4	1.224	37.1	56.5	7.188	36.0
-20	430	5.5	4.36	13.0	6.5	170/105	116	1.74	2000	4.5	21.0	12.07							
-10	400	6.0	4.32	16.0	10.0	165/100	102	1.72	2200	2.0	21.0	11.73							
0	420	10.0	5.12	14.0	12.0	185/110	114	1.43	2300	4.5	20.0	10.93	59.9	48.1	7.235	35.6	56.1	7.196	34.8
10	410	10.0	3.40	12.0	11.0	170/90	122	1.95	1700	7.5	25.0	11.92							
20	390	12.5	3.15	16.0	12.0	175/90	91	1.04	900	15.0	23.0	22.12	71.7	43.1	7.267	30.5	54.3	7.211	36.7
30	420	13.5	5.67	16.0	12.0	145/80	130	1.18	950	11.5	17.0	14.41							
40	410	15.0	6.03	14.0	12.0	160/85	110	1.52	1100	7.0	19.5	8.22	62.2	42.6	7.280	38.2	52.8	7.226	36.5
50	430	14.5	6.22	14.0	11.0	165/95	114	1.70	1350	6.0	19.5	8.33							
60	410	16.5	5.12	13.0	5.5	170/105	120	1.32	1450	5.0	18.0	8.55	76.2	39.1	7.342	41.9	50.3	7.256	40.0
70	430	15.5	5.12	13.0	5.5	175/100	114	1.66	1525	5.0	18.5	8.33							
80	390	17.5	5.18	15.0	6.0	170/100	130	1.64	1550	4.5	19.0	8.09	81.8	34.9	7.344	38.8	46.1	7.281	41.3
90	390	17.5	5.65	14.0	7.0	170/100	130	1.62	1600	3.0	11.5	9.10							
100	400	17.5	4.90	13.0	7.0	165/95	121	1.47	1550	2.0	13.0	9.37	72.8	36.3	7.353	36.6	44.8	7.278	42.5
110	410	17.0	4.93	14.0	7.0	160/90	126	1.54	1550	2.5	11.5	8.38							
120	430	15.5	5.76	13.0	7.0	160/90	140	1.26	1500	2.5	11.0	8.13	63.7	37.5	7.315	35.7	47.4	7.268	43.0

DRUG WR6026 WT 9.77 kg

DOSE 4.0 [illegible]/kg/min DATE 11/23/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	175/[illegible]	196	2.01	3550	4.0	12.0	5.97	79.4	[illegible]	7.413	44.4	36.9	7.385	36.5
-20	[illegible]	15.0	5.34	16.0	[illegible]	[illegible]	300	1.94	3500	3.0	11.0	5.56							
-10	[illegible]	[illegible]	[illegible]	16.0	[illegible]	[illegible]	304	1.85	[illegible]	[illegible]	12.0	6.59							
0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.10	[illegible]	[illegible]	10.0	5.88	84.3	[illegible]	[illegible]	42.7	31.0	7.380	36.7
10	[illegible]	[illegible]	8.10	[illegible]	[illegible]	[illegible]	180	1.65	3000	4.0	10.0	6.06							
20	[illegible]	[illegible]	[illegible]	[illegible]	.8	[illegible]	[illegible]	[illegible]	[illegible]	9.0	14.0	11.67	[illegible]	[illegible]	7.415	40.0	35.7	7.364	34.7
30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	10.0	[illegible]	8.66							
40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8.60	[illegible]	33.6	[illegible]	40.9	39.7	7.320	35.8
50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	6.5	[illegible]	[illegible]							
60	[illegible]	18.0	[illegible]	[illegible]	[illegible]	[illegible]	162	[illegible]	2400	7.0	11.0	8.66	78.4	[illegible]	[illegible]	40.1	[illegible]	7.305	37.0
70	[illegible]	18.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2325	7.0	10.0	8.47							
80	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	8.0	7.89	[illegible]	[illegible]	7.366	36.1	44.1	7.301	37.8
90	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8.5	8.50							
100	[illegible]	20.0	[illegible]	8.0	.8	[illegible]	[illegible]	[illegible]	[illegible]	9.5	9.0	8.82	75.9	[illegible]	[illegible]	33.5	44.9	[illegible]	38.0
110	[illegible]	20.0	[illegible]	[illegible]	.8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8.0	8.53							
120	[illegible]	[illegible]	7.98	[illegible]	[illegible]	[illegible]	180	0.97	[illegible]	[illegible]	9.0	9.8	78.9	[illegible]	[illegible]	28.6	43.7	7.313	40.0

DRUG WR-6026 WT 11.59 kg

DOSE 4.0 μmol/kg/min DATE 10/26/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	310	13	4.03	58.0	1.0	170/—	180	1.98	3400	4.0	12.0	6.06	74.0	42.9	7.333	40.3	47.3	7.315	33.3
-20	310	9.0	2.79	62.0	1.5	—/120	156	1.90	3200	1.5	12.0	6.32							
-10	350	8.5	2.98	54.0	1.5	—/—	156	1.78	3300	1.0	11.0	6.18							
0	330	8.5	2.80	50.0	1.5	—/—	180	1.79	3300	1.5	11.0	6.14	69.8	41.2	7.332	41.5	46.7	7.296	31.5
10	320	9.5	3.04	41.0	2.0	170/115	176	2.08	1900	5.0	16.0	7.69							
20	345	12.0	4.14	43.0	2.0	155/105	156	1.44	1050	7.0	19.0	13.19	74.1	37.0	7.341	44.7	49.9	7.319	40.5
30	330	12.0	4.36	44.0	1.6	—/130	148	1.76	1325	7.0	16.0	9.09							
40	330	12.0	4.16	42.0	1.0	170/120	178	1.76	1050	5.0	13.0	7.43	78.1	38.8	7.364	44.7	40.4	7.329	35.8
50	330	12.0	4.18	44.0	1.5	—/125	178	2.01	1800	3.5	10.2	5.06							
60	340	14.5	5.26	44.0	1.0	170/105	152	2.07	1925	3.0	10.0	4.83	76.9	34.9	7.386	32.3	38.9	7.363	34.5
70	345	14.5	5.00	43.0	1.0	170/105	168	2.10	3300	2.0	9.0	4.28							
80	350	14.5	5.25	42.0	1.0	170/115	156	2.32	3750	3.0	12.0	5.33	76.1	37.7	7.376	33.9	36.9	7.369	36.8
90	340	16.0	5.80	44.0	1.0	165/110	172	2.36	3750	2.0	11.5	4.87							
100	340	18.0	5.88	44.0	1.0	170/120	168	2.32	4250	3.0	13.0	6.44	71.7	34.7	7.389	38.9	46.1	7.368	38.0
110	330	17.5	5.60	32.0	1.0	170/120	172	2.32	3450	4.0	14.5	6.01							
120	320	17.0	5.61	33.0	1.0	170/115	164	2.31	3350	3.0	15.0	6.70	72.5	37.7	7.378	37.3	37.9	7.362	36.2

DRUG WR-6026 WT 8.64 kg

DOSE 4.0 mmole/kg/min DATE 8/4/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	3.00	11.0	3.30	17.8	22.8	78	164	1.89	1200	-3.0	8.0	4.23	69.5	37.4	7.385	41.4	42.1	7.208	21.5
-20	3.00	11.0	3.30	18.2	22.8	78	200	1.66	1160	-1.5	8.5	5.12							
-10	1.64	17.0	2.80	18.1	22.8	82	226	1.64	1080	-3.0	7.0	4.27							
0	2.00	15.0	2.40	16.2	22.8	82	165	1.50	1080	-3.0	6.0	4.00	67.5	35.1	7.467	39.9	46.1	7.183	26.0
10	1.70	28.0	3.36	16.2	22.8	78	156	1.47	1160	1.0	7.0	4.76							
20	1.80	42.0	3.24	19.0	22.8	76	148	1.57	1240	-1.0	9.0	5.96	72.9	36.1	7.390	41.9	38.6	7.234	26.7
30	1.80	45.0	3.24	18	22.8	74	150	1.64	1160	1.0	8.0	4.88							
40	1.80	42.0	3.24	18	22.8	74	148	1.65	1160	-1.0	7.5	4.54	72.9	34.2	7.379	47.5	39.3	7.280	27.5
50	1.80	42.0	3.24	18	22.8	74	150	1.44	1120	-1.0	6.0	4.17							
60	1.80	42.0	3.24	18	22.8	74	148	1.31	1160	1.5	5.5	4.20	69.1	39.3	7.365	43.5	41.0	7.182	27.8
70	1.80	41.0	4.44	18.9	22.8	0	148	1.30	1160	1.5	4.5	3.57							
80	1.80	26.5	4.68	18	22.8	78	148	1.35	1160	-2.0	4.5	3.61	72.1	37.4	7.385	39.7	45.3	7.189	27.0
90	1.80	32.0	4.80	17.8	22.8	78	148	1.15	1120	-2.0	4.0	3.48							
100	1.80	36.5	4.68	18.9	22.8	78	148	1.15	1120	-2.0	3.5	3.12	71.2	34.1	7.387	43.1	45.3	1.177	25.0
110	1.80	36.5	4.68	18.8	22.8	78	148	1.00	1120	-1.5	3.5	3.24							
120	1.80	36.5	4.68	18.8	22.8	78	148	1.00	1120	-1.5	3.5	3.36	71.2	32.4	7.397	41.6	45.4	7.181	24.5

DRUG WR-6026 WT 9.54kg

DOSE ~~4.0 mg/kg/min~~ DATE 9/15/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A Po_2	A Pco_2	A pH	V Po_2	V Pco_2	V pH	HCT
-30																			
-20																			
-10																			
0																			
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

DRUG Trimaquine H_3PO_4 WT 10.2kg

DOSE 0.5 mole/kg/min DATE 1/12/84

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	1.0	20	1.0	50.0		90/50	208	1.71	3200	3.5	17.5	10.23	65.8	46.9	1.357	45.1	51.2	7.317	49.0
-20	0.1	20	1.7	17.0	0.6	90/55	204	1.75	3550	3.5	15.0	8.57							
-10	2.5	23.5	1.9	18.2	1.5	90/60	204	1.95	3000	4.0	14.0	7.18							
0	2.5	21.5	1.1	11.2	1.5	90/50	204	2.05	3600	4.0	15.0	7.32	17.6	41.2	7.312	51.4	46.3	7.344	50.0
10	2.5	22.0	3.4	15.0	1.5	90/55	204	2.26	3565	5.5	14.5	6.42							
20	2.0	21.0	4.2	14.0	1.5	90/55	204	2.34	3500	6.0	15.0	6.41	18.6	41.2	7.458	45.0	40.6	7.407	49.7
30	2.5	22.5	4.0	19.4	2.0	90/55	210	2.22	3750	6.0	12.5	6.08							
40	2.0	19.0	3.0	15.6	2.0	90/55	196	2.42	3850	4.0	14.5	5.99	65.5	37.9	7.340	47.5	43.8	7.333	51.7
50	2.5	17.1	2.9	12.5	1.5	90/55	194	2.19	3200	4.5	13.0	7.01							
60	2.0	20.0	3.4	14.0	1.5	90/55	202	2.88	3600	4.0	17.5	5.03	73.7	32.8	7.382	24.9	44.2	7.452	57.3
70	2.5	22.5	3.8	15.6	1.5	90/55	198	2.26	3400	4.0	13.0	6.25							
80	2.5	16.2	2.6	10.3	2.0	90/55	220	2.28	3100	3.5	11.5	6.42	70.4	34.4	7.38	42.2	48.5	7.356	48.8
90	2.5	16.5	2.61	12.1	2.0	90/55	220	1.71	2845	4.0	11.0	6.45							
100	2.0	20.5	3.42	15.2	1.5	90/55	210	1.44	3700	5.0	11.0	7.38	64.5	39.5	7.35	42.2	44.0	7.357	48.5
110	2.0	21.5	4.04	18.2	2.0	90/55	214	1.62	3600	5.0	11.5	8.10							
120	2.5	20	3.80	17.7	2.0	90/55	210	1.46	3450	5.0	11.5	7.88	57.4	42.0	7.38	40.4	44.2	7.351	48.2

DRUG Innovar-$H_2P_{O_4}$ WT 9.45 kg

DOSE ~~0.5 mcg/kg/min~~ DATE 12/13/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	[illegible]	33.0	4.5	18.0	[illegible]	100/110	168	1.76	3750	5.0	13.0	7.39	89.7	37.0	7.360	37.9	43.3	7.327	35.3
-20	[illegible]	24.0	5.8[illegible]	19.0	3.[illegible]0	100/[illegible]	164	1.85	3850	5.0	12.5	6.76							
-10	[illegible]	24.0	5.8[illegible]	19.[illegible]	3.[illegible]	[illegible]/[illegible]	164	1.94	4300	4.5	13.0	6.70							
0	[illegible]	18.0	4.[illegible]9	9.0	3.0[illegible]	[illegible]/95	164	1.70	4000	5.0	13.0	7.65	72.0	32.8	7.369	46.4	39.0	7.270	39.0
10	[illegible]	34.5	5.76	17.0	-	110/90	132	1.69	3600	4.5	12.0	7.10							
20	[illegible]	35.5	7.31	21.0	-	[illegible]/90	128	1.49	3400	4.0	11.0	7.38	80.3	30.3	7.385	38.2	38.6	7.334	35.3
30	1.40	41.0	6.[illegible]6	21.0	-	95/90	130	1.15	2300	5.0	10.0	8.70							
40	1.[illegible]	39.5	5.97	22.0	-	[illegible]/85	120	1.30	1850	7.0	13.0	10.83	70.6	37.4	7.[illegible]0	40.4	44.0	7.261	39.0
50	1.[illegible]	36.5	6.[illegible]	24.0	-	6[illegible]/90	122	1.16	2050	6.5	12.5	10.78							
60	1.[illegible]	33.0	5.[illegible]	26.0	-	[illegible]/[illegible]	94	0.[illegible]	1800	6.0	11.5	11.98	66.9	40.9	7.[illegible]3	34.2	47.7	7.[illegible]0	40.0
70	1.[illegible]	38.0	5.[illegible]9	28.0	-	[illegible]/[illegible]	88	0.91	1[illegible]0	6.0	11.5	12.64							
80	1.[illegible]	41.0	6.[illegible]6	30.0	-	[illegible]/[illegible]	88	0.9[illegible]	1450	5.0	9.5	10.11	70.6	40.4	7.[illegible]5	33.7	50.2	7.224	41.0
90	1.[illegible]	37.5	6.[illegible]9	31.0		[illegible]/60	[illegible]	1.04	1450	5.0	9.5	9.13							
100	1.[illegible]	34.[illegible]	5.[illegible]6	16.0	-	[illegible]/[illegible]	88	1.06	1600	4.0	10.0	9.43	74.[illegible]	36.8	7.299	37.2	49.3	7.234	40.0
110	1.[illegible]	33.0	5.[illegible]4	14.0	-	[illegible]/[illegible]	88	1.04	1630	3.5	10.0	9.62							
120	1.[illegible]	31.0	6.20	15.0	-	[illegible]/[illegible]	96	1.11	1800	3.0	8.5	7.66	75.3	33.[illegible]	7.3[illegible]	38.2	47.8	7.249	40.5

DRUG ~~Isoproterenol HCl~~ WT 10.68 kg

DOSE ~~0.5 mcg/kg/min~~ DATE 11/8/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	320	[illegible]	1.72	16.0	1.5	[illegible]	176	1.92	-100	3.0	12.0	6.25	80.1	39.5	7.332	41.2	47.9	7.301	39.2
-20	310	5.0	1.55	16.0	[illegible]	[illegible]	168	1.86	-200	3.0	11.0	5.91							
-10	300	4.5	1.35	16.0	[illegible]	[illegible]	164	1.85	-200	3.0	11.0	5.73							
0	310	4.5	1.36	16.0	[illegible]	[illegible]	168	1.97	-200	4.0	11.0	5.58	71.5	46.2	7.286	43.5	48.8	7.258	39.5
10	290	5.0	1.45	16.0	[illegible]	[illegible]	156	1.79	-300	6.0	14.0	7.82							
20	310	5.5	1.70	[illegible]	[illegible]	[illegible]	152	1.80	-200	5.5	10.0	5.56	66.9	46.3	7.281	46.5	49.6	7.265	39.8
30	310	5.5	1.87	16.0	[illegible]	[illegible]	[illegible]	1.96	-100	6.0	7.5	3.83							
40	310	6.0	1.87	16.0	[illegible]	[illegible]	[illegible]	2.02	-100	7.0	10.0	4.81	65.1	46.1	7.312	43.6	46.9	7.293	40.7
50	310	6.5	[illegible]	16.0	[illegible]	[illegible]	[illegible]	2.08	[illegible]	8.0	10.0	4.81							
60	310	[illegible]	1.86	16.0	[illegible]	[illegible]	[illegible]	2.00	-100	10.0	11.0	5.50	63.6	44.2	7.310	45.0	46.5	7.261	43.8
70	310	5.0	1.55	16.0	[illegible]	[illegible]	[illegible]	2.08	[illegible]	4.5	10.5	5.05							
80	310	5.5	1.70	16.0	[illegible]	[illegible]	[illegible]	1.88	-200	4.0	11.0	5.85	60.1	45.0	7.278	47.3	46.7	7.268	45.2
90	310	5.0	1.85	[illegible]	[illegible]	[illegible]	[illegible]	1.70	-100	4.0	10.0	5.88							
100	310	6.0	[illegible]	16.0	[illegible]	[illegible]	[illegible]	1.69	-200	3.5	10.0	5.92	67.5	37.7	7.354	49.8	42.5	7.293	44.8
110	[illegible]	4.0	[illegible]	16.0	[illegible]	[illegible]	141	1.56	-400	1.0	9.5	6.09							
120	[illegible]	5.0	[illegible]	16.0	[illegible]	[illegible]	143	1.62	-400	3.0	9.5	6.25	63.7	44.7	7.349	49.9	51.9	7.295	43.3

DRUG Bupivacaine HCl WT 15.23 kg

DOSE 0.5 mg/kg/min DATE 10/14/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30								1.60	2000	-0.5	7.0	4.37	94.5	44.9	7.339	47.5	49.1	7.306	33.7
-20		8.5						1.70		0.0	7.0	4.12							
-10										-1.0	7.0	4.32							
0										0.0	8.0	5.76	98.4	44.9	7.319	43.5	51.9	7.300	33.5
10								1.70			10.0	5.88							
20								2.16			10.5	4.86	98.8	41.9	7.361		53.2		
30								1.61		1.0	10.0	5.52							
40										-0.5	6.0	5.70	84.5	46.4	7.316	41.5	54.8		
50										1.0	7.0	4.34							
60																			
70								1.80		1.0	8.0	4.44							
80											12.0	5.94							
90								1.97			11.0	5.18							
100																			
110																			
120																			

DRUG Primaquine H_3PO_4 WT 9.54 kg

DOSE ~~.25 mg/kg bolus~~ DATE 5/25/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A Po_2	A Pco_2	A pH	V Po_2	V Pco_2	V pH	Hct
-30	[illegible]	7.0	1.56	8.0	[illegible]	[illegible]	184	2.06	2350	0.0	25.0	12.14	57.0	48.6	1.249	42.1	61.6	7.240	37.0
-20	[illegible]	6.5	1.30	[illegible]	[illegible]	[illegible]	184	1.92	2300	0.0	24.0	12.50							
-10	[illegible]	7.0	[illegible]	[illegible]	[illegible]	[illegible]	180	1.76	2300	0.0	23.0	11.73							
0	[illegible]	7.0	[illegible]	96.0	[illegible]	[illegible]	176	1.94	2300	-0.5	21.0	10.82	68.3	48.1	7.235	50.2	49.2	7.225	38.2
10	[illegible]	7.5	[illegible]	[illegible]	[illegible]	[illegible]	158	1.65	1700	0.0	15.5	9.39							
20	[illegible]	10.0	[illegible]	44.0	[illegible]	[illegible]	156	1.52	1550	0.0	8.5	5.59	84.1	43.7	7.260	51.7	48.2	7.228	37.2
30	[illegible]	9.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.52	1675	-0.5	6.0	3.95							
40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	160	1.52	1600	-1.0	6.0	3.95	82.8	43.7	7.271	47.5	48.3	7.258	38.5
50	[illegible]	8.5	[illegible]	44.0	[illegible]	[illegible]	152	1.48	1450	-0.5	6.5	4.39							
60	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	140	[illegible]	1400	0.0	7.5	5.14	55.7	49.6	7.212	49.0	49.7	7.198	38.0
70	[illegible]	8.0	[illegible]	[illegible]	[illegible]	[illegible]	144	1.43	1400	-1.0	6.0	4.20							
80	[illegible]	9.0	[illegible]	[illegible]	[illegible]	[illegible]	148	1.42	1400	-0.5	6.0	4.22	85.6	43.7	7.252	52.1	51.1	7.228	38.2
90	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	148	1.33	1250	-0.5	6.0	4.57							
100	[illegible]	13.0	[illegible]	[illegible]	[illegible]	[illegible]	140	1.12	1150	-1.0	5.0	4.46	88.9	40.7	7.281	44.3	49.3	7.240	37.5
110	[illegible]	15.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.16	925	-1.5	4.0	3.77							
120	[illegible]	16.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	975	-1.5	3.5	3.40	91.4	34.3	7.301	40.8	45.9	7.250	36.3

6TT

DRUG Procaine-HCl PO4 WT 16.82kg

DOSE 25 mcg/kg/min DATE 8/23/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30													80.5	40.2		38.8			31.0
-20																			
-10																			
0													66.4	49.0		35.7		7.211	33.8
10																			
20													73.8	47.9		43.5		7.204	33.5
30																			
40													75.1			44.1		7.219	
50																			
60													88.7			41.1			
70																			
80													86.1			31.8		7.21	
90																			
100													87.3			34.2		7.219	40.0
110																			
120													92.7					7.252	40.0

120

DRUG Tranexamic Hx PO4 WT 14.09kg

DOSE 10mg/kg bolus DATE 1/10/84

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	2.5	40	1.27	17.3	4.4	75/25	150	2.45	2300	5.0	17.0	7.00	45.4	52.4	7.238	36.8	52.3	7.248	44.2
-20	3.40	50	1.25	6.80	8.0	80/35	70	2.52	1900	6.0	17.0	7.26							
-10	2.05	35	1.61	17.5	13.5	75/25	50	2.50	2000	6.0	16.5	7.17							
0	2.70	35	1.57	21.8	18.3	75/25	120	2.78	2300	5.0	17.0	6.85	63.3	46.4	7.270	44.1	53.2	7.247	45.8
10	3.10	45	1.96	15.6	7.0	80/30	130	2.36	2000	9.0	17.0	8.05							
20	2.15	55	1.67	14.0	7.0	80/30	170	2.10	1950	7.0	17.0	8.10	78.2	41.9	7.297	45.4	50.6	7.260	44.3
30	2.25	45	1.77	15.2	6.2	80/35	160	2.20	2100	7.0	13.0	5.72							
40	3.10	45	1.75	23.1	6.5	80/30	170	2.30	2.20	7.0	13.0	5.65	67.7	43.2	7.290	46.0	48.8	7.274	45.5
50	3.20	55	1.75	20.1	5.7	80/35	160	2.52	2350	9.0	13.5	5.93							
60	3.0	50	1.55	16.7	5.7	80/32	150	2.51	2250	7.0	13.0	5.18	77.7	40.1	7.316	48.3	47.0	7.288	47.2
70	2.60	45	1.70	22.2	6.1	80/35	150	2.66	2300	7.0	13.0	4.89							
80	2.05	45	1.32	22.0	7.5	80/32	120	2.46	2350	6.0	6.5	2.77	71.7	44.7	7.296	52.2	45.9	7.300	47.2
90	3.40	55	1.86	21.1	7.0	80/33	170	2.53	2300	8.0	11.0	4.42							
100	2.15	45	1.92	21.2	7.5	80/30	150	2.38	2.50	6.5	6.0	2.77	71.2	43.9	7.300	50.0	45.1	7.300	48.0
110	3.10	50	1.75	21.0	9.7	80/35	150	1.71	2.22	7.0	11.0	5.76							
120	2.15	55	2.17	20.1	9.7	80/30	150	2.76	2300	7.0	11.5	6.53	73.2	41.9	7.319	47.3	45.1	7.309	48.2

DRUG Trimaquine-HCl WT 4.32kg

DOSE 40 μg/kg/min DATE 12/22/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
30	325	4.5	1.46	37.3	18.5	135/50	144	2.05	2550	4.0	26.0	12.86	65.5	48.9	7.161	38.3	38.3	7.116	40.5
20	280	4.0	1.12	31.1	17.3	135/50	120	2.09	2600	5.5	28.5	13.64							
10	315	4.5	1.38	32.8	14.6	140/55	116	2.10	2800	5.0	27.0	12.86							
0	240	4.0	1.16	30.0	27.6	130/50	124	1.97	2800	5.0	28.0	14.21	59.3	54.0	7.151	36.5	38.5	7.094	41.8
10	310	5.0	1.56	31.7	18.4	130/40	138	1.98	2300	6.0	27.5	13.89							
20	320	6.0	1.87	30.6	15.8	130/40	148	1.94	2100	6.0	25.0	12.89	63.2	57.4	7.164	42.9	42.9	7.121	37.5
30	345	5.0	1.72	29.9	18.3	130/55	142	1.86	2300	5.0	27.5	14.78							
40	330	5.5	1.82	30.6	15.1	130/50	130	1.82	2000	4.0	23.0	12.64	63.4	53.2	7.169	40.2	40.2	7.137	37.8
50	335	5.5	1.83	29.8	15.1	130/50	120	1.68	1850	4.5	22.0	13.10							
60	325	6.0	1.96	29.3	15.3	130/50	126	1.70	1700	4.0	18.5	10.88	73.5	42.6	7.233	37.9	37.9	7.160	36.8
70	320	8.0	2.54	32.3	18.4	140/60	140	1.57	1750	3.5	16.0	10.19							
80	315	8.0	2.54	31.0	17.5	140/60	144	1.57	1725	4.0	14.0	8.92	76.1	42.0	7.211	36.5	36.5	7.202	34.0
90	345	9.5	3.11	32.7	14.7	130/55	132	1.52	1800	3.5	14.0	9.21							
100	290	7.0	2.01	35.6	20.1	135/55	142	1.63	1800	4.0	23.0	14.17	62.6	45.1	7.231	38.1	38.1	7.211	34.3
110	360	5.0	1.79	36.3	22.0	135/60	127	1.65	1835	4.0	26.0	15.76							
120	335	6.0	2.01	35.9	22.3	140/60	132	1.86	1800	5.0	23.0	12.36	65.6	47.6	7.217	36.9	36.9	7.171	37.2

DRUG Dimethylaminoethyl WT 13.18kg

DOSE 10 mcg/kg/min DATE 11/2/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	5.0	3.0	1.47	34.0	2.5	160/100	158	1.99	1700	5.5	13.0	8.78	66.4	44.0	7.345	37.9	60.3	7.272	42.5
-20	6.5	3.0	1.87	44.0	3.0	150/100	146	1.92	1800	5.0	13.5	8.88							
-10	6.5	3.5	1.99	50.0	3.0	150/100	140	1.74	1800	6.0	14.0	8.04							
0	6.0	3.0	1.94	50.0	4.0	150/100	138	1.84	1900	6.0	15.0	8.15	55.3	41.1	7.265	36.8	56.5	7.260	43.0
10	5.5	3.0	1.43	50.2	2.5	150/100	132	1.72	1600	8.0	19.0	8.96							
20	5.5	4.5	2.47	34.0	2.0	150/100	168	1.89	1700	6.0	14.0	7.41	52.0	40.	7.360	41.2	56.0	7.244	43.0
30	5.0	5.0	2.76	36.0	2.5	150/100	172	1.92	1700	6.0	16.0	6.65							
40	5.5	6.0	3.29	41.0	2.5	150/100	142	1.77	1600	5.0	14.0	6.21	51.3	39.1	7.289	35.7	53.7	7.286	45.2
50	5.5	6.0	3.33	46.0	2.5	150/100	168	1.80	1600	6.0	12.0	6.67							
60	5.80	6.5	3.76	50.0	4.0	150/100	178	1.68	1500	4.0	12.0	7.14	97.2	43.5	7.367	29.5	50.7	7.304	44.3
70	5.5	5.5	3.04	55.2	6.0	150/100	176	1.84	1400	5.0	13.5	6.34							
80	6.0	5.0	3.62	72.0	5.5	150/100	158	1.46	1400	5.5	14.0	9.59	73.1	41.5	7.362	33.9	50.8	7.292	45.3
90	6.5	6.0	3.63	60.0	3.0	150/100	158	1.26	1400	5.5	14.0	11.11							
100	7.5	5.0	3.26	65.2	2.0	150/100	162	1.46	1350	8.0	14.0	12.07	66.3	38.4	7.450	33.0	48.5	7.314	44.3
110	7.2	6.0	3.67	72.0	3.0	150/100	158	1.62	1300	6.0	14.0	11.48							
120	7.5	8.0	3.81	72.0	2.5	150/100	150	1.20	1200	6.0	13.0	11.67	66.1	39.3	7.436	29.0	49.0	7.351	44.5

DRUG Trimazosine H_3PO_4 WT 12.27 kg

DOSE [illegible] DATE 9/20/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	$\overline{PAP}$	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	12.5	6.07	86.1	41.8	7.343	40.8	54.4	7.281	27.2
-20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	160	[illegible]	[illegible]	[illegible]	13.0	6.31							
-10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	11.5	5.42							
0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2000	[illegible]	14.0	6.86	97.6	40.7	7.342	50.9	47.0	7.301	29.8
10	[illegible]	4.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2.16	[illegible]	[illegible]	15.0	6.94							
20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.99	[illegible]	[illegible]	17.0	8.34	84.3	47.0	7.289	47.5	51.6	7.276	30.0
30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	16.0	7.80							
40	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	4.5	[illegible]	7.69	81.4	43.7	7.318	44.5	52.3	7.277	28.3
50	[illegible]	4.5	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4.0	15.0	7.94							
60	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4.0	[illegible]	[illegible]	81.6	48.4	7.240	44.3	52.7	7.276	28.0
70	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	13.5	7.46							
80	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	16.0	[illegible]	72.1	49.8	7.277	43.5	53.1	7.266	28.2
90	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	16.0	9.76							
100	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	89.9	45.6	7.309	35.5	57.3	7.259	29.0
110	[illegible]			[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	17.0	11.80							
120	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	77.4	51.9	7.258	38.4	60.1	7.226	28.5

DRUG Lidocaine HCl WT 11.14kg

DOSE 40 mcg/kg/min DATE 9/13/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30		15	111		8				1000	2.0	19.0	8.88	44.8	- ③	7.337	39.1	- ③	7.214	③ -
-20		6.5							3000	0.0	12.5	5.90							
-10					6				3000	1.0	11.5	5.36							
0		10							3000	0.0	17.5	7.71	66.1	-	7.208	41.2	-	7.193	-
10		8.0							3000	1.0	13.0	5.85							
20		13.0							3000	1.0	16.5	7.34	87.5	-	7.376	34.9	-	7.225	-
30		12.5							3000	0.5	11.5	5.23							
40		16.5							3000	0.5	9.5	5.97	80.8	-	7.339	32.1	-	7.245	-
50		16.5							2775	0.5	6.0	3.00							
60		12.0							3000	0.5	7.0	3.84	74.0	-	7.38	31.5	-	7.260	-
70		6.5							2800	0.0	7.5	3.38							
80		9.0							3000	1.5	10.0	5.32	60.7	-	7.32	38.8	-	7.247	-
90		11.5							3000	0.5	8.5	4.54							
100		14.0							3000	1.0	9.5	4.84	75.2	-	7.32	32.3	-	7.264	-
110		13.0							3000	1.0	10.5	5.71							
120		14.0							2775	0.0	11.0	6.04	65.9	-	7.340	40.0	-	7.224	-

DRUG [illegible] WT 10.45 kg

DOSE [illegible] DATE 8/12/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	DP/DT	PWP	$\overline{PAP}$	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
-30	[illegible]	7.0	[illegible]	[illegible]	11.0	[illegible]	[illegible]	1.58	1100	0.5	13.0	8.2?	73.5	41.6	[illegible]	38.9	47.0	7.249	36.5
-20	[illegible]	7.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.5	11.5	[illegible]							
-10	[illegible]	[illegible]	[illegible]	1.8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	-1.0	8.0	12.70							
0	[illegible]	7.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.10	[illegible]	0.5	7.5	6.8?	75.5	40.6	?.277	33.4	52.2	7.203	35.0
10	[illegible]	[illegible]	[illegible]	?.8		[illegible]	[illegible]	1.16	[illegible]	1.5	8.0	6.90							
20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.09	[illegible]	[illegible]	10.0	7.17	90.7	?6.9	?.288	42.1	48.5	7.226	36.0
30	[illegible]	16.0	[illegible]	?.8		[illegible]	[illegible]	[illegible]	880	?.5	7.0	7.56							
40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9.5	8.72	76.4	[illegible]	7.313	41.8	46.3	7.249	36.7
50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9.5	[illegible]							
60	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	?1.9	[illegible]	38.5	[illegible]	7.232	36.5
70	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.5	[illegible]							
80	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	8.0	[illegible]	87.9	?8.9	[illegible]	37.5	[illegible]	7.188	40.5
90	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	?.0	[illegible]	[illegible]							
00	[illegible]	18.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9.76	97.7	[illegible]	?.214	44.6	49.3	[illegible]	37.3
110	[illegible]	16.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	10.00							
20	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	1.5	7.5	10.14	[illegible]	[illegible]	[illegible]	44.8	46.6	[illegible]	37.8

DRUG Trimetaphan 4mg/kg WT 2.54 kg

DOSE 4.75 mcg/kg/min DATE 12/21/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	HCT
30	290	5.5	1.60	21.0	7.0	170/—	164	1.82	2500	4.5	17.0	9.34	51.1	49.3	7.311	45.3	48.7	7.327	41.2
20	280	6.0	1.71	21.0	5.0	170/0	140	1.72	2300	6.0	15.0	8.72							
10	270	7.5	1.40	20.0	5.5	165/0	160	1.60	2200	4.0	14.0	8.75							
0	280	6.0	1.68	18.5	4.0	155/0	150	1.47	2100	3.5	11.5	7.82	69.3	43.6	7.327	50.1	47.6	7.324	41.5
10	250	7.5	1.87	20.0	5.0	155/65	168	1.46	1700	6.0	11.5	7.88							
20	260	14.5	3.19	21.0	2.0	165/75	152	1.70	1800	8.0	11.5	6.76	80.5	40.7	7.360	44.4	45.6	7.343	39.0
30	248	16.0	3.76	20.0	3.0	170/0	160	1.62	2125	5.5	10.0	6.17							
40	235	9.0	2.07	18.0	7.0	165/—	154	1.64	1950	7.0	12.0	7.32	65.0	48.0	7.307	50.0	47.3	7.314	41.3
50	235	8.0	1.88	17.5	5.5	170/75	166	1.64	2000	-	14.5	8.84							
60	240	8.0	1.92	17.0	6.0	170/—	176	1.62	2100	-	14.0	8.64	75.6	45.6	7.330	51.2	48.3	7.318	41.8
70	234	8.0	1.96	17.5	8.0	170/—	180	1.50	1850	-	9.5	6.33							
80	260	9.0	2.34	19.0	7.0	170/—	156	1.37	1700	-	8.0	5.84	78.4	41.1	7.368	48.3	46.5	7.287	41.8
90	240	11.0	2.64	20.0	6.0	170/—	164	1.25	1500	-	8.0	6.40							
100	230	12.5	2.88	17.0	6.0	170/0	140	1.18	1475	-	8.5	7.20	75.0	29.2	7.341	48.3	45.1	7.347	41.5
110	210	9.0	1.89	15.0	7.0	165/60	135	1.11	1250	-	10.0	9.01							
120	200	10.5	2.10	14.8	7.0	160/0	140	1.12	1200	-	9.5	8.48	76.8	42.4	7.357	47.3	46.5	7.329	41.0

DRUG Vecuronium 4 Pkg WT 19.42kg

DOSE 1.25 mcg/kg/min DATE 11/30/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
30	285	9.5	2.71	6.0	2.0	[illegible]	148	1.81	3200	4.5	19.0	10.33	71.0	47.0	7.316	47.5	49.1	7.306	40.0
20	240	9.5	2.28	6.0	1.5	[illegible]	184	1.94	3500	4.5	17.5	9.02							
10	285	10.0	2.85	17.0	1.5	[illegible]	116	1.92	2700	4.0	17.0	8.85							
0	240	8.5	2.04	6.0	1.5	[illegible]	122	1.86	3300	4.0	16.0	8.60	66.7	45.0	7.317	37.4	48.9	7.308	40.0
10	200	12.0	2.40	12.0	1.5	[illegible]	116	1.82	1800	6.0	15.0	8.24							
20	150	15.5	2.32	15.0	1.5	[illegible]	116	1.88	1600	7.5	17.5	9.31	76.9	41.6	7.350	40.8	44.1	7.304	40.0
30	245	11.0	2.70	11.0	1.5	[illegible]	119	2.07	1900	6.0	19.0	10.78							
40	310	17.5	5.42	16.0	2.0	[illegible]	124	1.66	1450	-4	21.0	12.65	61.6	50.1	7.266	36.1	52.7	7.256	42.0
50	270	17.5	4.72	17.0	1.5	[illegible]	124	1.72	1600	-	22.0	12.41							
60	270	16.0	4.32	16.0	1.8	[illegible]	132	1.86	1710	-	22.0	11.83	62.7	47.4	7.326	34.5	56.2	7.256	42.0
70	270	14.0	3.78	14.0	2.0	[illegible]	124	1.64	1500	-	22.0	12.20							
80	285	15.0	4.27	14.0	1.5	[illegible]	124	1.64	1710	-	19.0	11.73	72.4	44.9	7.312	36.2	56.7	7.271	41.0
90	255	14.0	3.57	14.0	1.0	[illegible]	132	1.54	1450	-	20.0	12.97							
100	270	20.5	5.70	14.0	1.0	[illegible]	140	1.96	1600	-	19.0	9.69	78.2	38.8	7.360	36.2	52.5	7.287	37.3
110	280	16.0	4.48	14.0	2.0	[illegible]	124	1.60	1450	-	23.0	15.62							
120	290	15.5	4.49	14.0	1.8	[illegible]	130	1.84	1600	-	23.5	15.88	72.3	44.3	7.317	33.1	56.6	7.271	37.3

DRUG Inamrinone H_3PO_4 WT 9.04kg

DOSE 1.75 mcg/kg/min DATE 6/20/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
30								1.89					83.3						
20											8.0	4.65							
10											8.0	4.60							
0											7.0		64.0						
10											8.0								
20											8.0		71.0						
30											10.5								
40																			
50											9.5								
60											8.0		87.8						
70											6.5								
80											8.5	5.09	66.5						
90											8.5								
100											7.0								
110											9.0	6.00							
120											8.0								

DRUG Primaquine·H_3PO_4 WT 13.52 kg

DOSE 1.75 μmol/kg/min DATE 10/12/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	$\overline{PAP}$	PVR	A Po_2	A Pco_2	A pH	V Po_2	V Pco_2	V pH	HCT
-30																			
-20																			
-10																			
0																			
10																			
20																			
30																			
40																			
50																			
60																			
70																			
80																			
90																			
100																			
110																			
120																			

DRUG Primaquine H_3PO_4 WT 10.60 kg

DOSE 4.75 μmole/kg/min DATE 8/24/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
-30					6					0.5	10.0		56.4	58.3	7.185	33.1	62.5	7.164	31.2
-20										1.5	10.0	8.20							
-10										-1.0	10.0	8.40							
0										2.0	8.0	8.00	59.5	61.7	7.162	32.6	64.1	7.154	31.7
10										1.0	8.0	7.77							
20										2.5	8.0	6.06	77.2	53.4	7.198	48.2	62.1	7.161	27.7
30										3.0	7.0	5.00							
40										0.0	6.0	4.28	81.6	54.4	7.181	57.7	60.4	7.157	32.0
50										0.5	6.0	4.29							
60										1.5	6.5	4.64	76.3	58.1	7.147	50.9	62.7	7.122	34.7
70										0.0	7.0	4.76							
80										0.0	6.5	4.45	86.7	56.7	7.172	47.4	63.0	7.129	34.5
90										0.0	6.0	4.25							
100					5.4							5.69	84.3	56.3	7.172	42.2	70.2	7.127	37.2
110												4.84							
120					6.0							5.10	55.6	59.4	7.158	39.5	71.0	7.123	36.7

DRUG Lasamine HCl WT 12.73 kg

DOSE 1.75 mcg/kg/min DATE 8/19/83

TIME	TV	RESP	MV	C	R	ABP	HR	CO	dP/dT	PWP	PAP	PVR	A P_{O_2}	A P_{CO_2}	A pH	V P_{O_2}	V P_{CO_2}	V pH	Hct
30								1.57	760	1.5	13.0	8.44	79.5	44.8	1.411	48.3	43.0	7.252	38.0
20								1.35	970	1.5	12.0	8.00							
10								1.12	1040	1.5	10.5	7.39							
0								1.46	1000	1.5	9.5	6.57	101.2	38.4	1.319		41.6	7.284	
10								1.50	1000	1.5	10.0	6.67							
20								1.52	1.10	1.5	9.5	6.09	98.0		1.313		46.2	7.276	40.5
30								1.44	1040	1.5	8.0	5.40							
40										1.5	8.0	5.48	81.5			48.0	46.8	7.272	41.8
50										1.0	6.5	4.78							
60										0.5	6.5	4.45	76.3	38.4	1.320	46.8	41.1	7.283	40.2
70										0.0	6.5	4.71							
80										0.0	6.5	5.16	84.7	36.9	1.330	41.5	42.1	1.291	40.0
90										0.5	6.5	4.85							
100										1.0	6.5	5.56	77.8				45.8	7.265	
110										1.0	7.5	6.41							
120										1.0	7.5	7.21	85.1						

APPENDIX G

Blood Chemistry Performance

Data on Performance Evaluation are on file in the Departments of Pharmacology at the University of Tennessee College of Medicine and Walter Reed Army Institute of Research.

APPENDIX H

Certificate of Purity of Primaquine Diphosphate

Chemists Helping Chemists in Research and Industry

aldrich chemical company, inc.

ANALYTICAL DATA

Date January 3, 1983

Our: 16,039-3 Primaquine diphosphate, 99+%, GOLD LABEL

Batch No.: 2429BE

Analytical Results:

Appearance Orange powder

m.p. 205° dec. b.p.

n_D^{25} $[\alpha]_D$

Spectral Data:

I.R. Conforms to structure and standard as illustrated on page 1391 F of Edition III, of "The Aldrich Library of Infrared Spectra".

U.V.

N.M.R.

Assay:

V.P.C.

Titration 100.2% by NaOH titration

Other: The elemental analysis is as follows:

	C	H	N
Theory	39.56	5.98	9.23
Actual	38.47	5.85	9.11

SB/sdb

A. Napiorkowski

Anna Napiorkowski,
Quality Control Manager

45103

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SECTION II.

PROTOCOL

Determination of the Involvement of Histamine in the Blood Pressure Response to Liposome Carrier

Introduction

Liposome carrier suspension produces an arterial hypotension when given intravenously. In our recent studies, prior treatment with compound WR-149,024, reported to stabilize histamine-containing cells and antagonize factors which induce histamine release, appeared to reduce this hypotension. These findings have lead to the speculation that histamine is involved in this hypotensive response.

Rationale for Study

If release of histamine from body stores is responsible for the hypotension to liposome injections, a tachyphylaxis should develop as histamine stores are depleted. In dogs with chronically indwelling catheters to measure systemic and pulmonary arterial pressures, we could determine if repeated i.v. bolus injections of a given amount of liposome carrier suspension yield systemic or pulmonary arterial pressure responses which are progressively smaller.

Methods

Two male beagle dogs will be chronically fitted with both a Swan-Ganz balloon-tipped catheter into the pulmonary artery and a polyethylene cannula (PE 260) into the femoral artery to the level of the abdominal aorta. Measurement of pulmonary arterial and wedge pressure and cardiac output will be obtained using the Swan-Ganz catheter with features for thermal dilution determinations. Systemic blood pressure will be measured via the femoral arterial cannula externalized to the nape of the neck. Dogs will be maintained on 100 units/kg/day Na-heparin (s.c.) twice a day to prevent thrombosis. After a seven day period of recovery, the following experiments will be performed.

Dogs will be anesthetized with Na-pentobarbital (30 mg/kg, i.v.) and allowed to reach a steady state of anesthesia at which stable control values can be obtained for pulmonary artery, pulmonary wedge, and systemic blood pressure and heart rate. Bolus i.v. doses of 1.0 ml of liposome carrier will be given via a butterfly-type cannula in a cephalic vein over a period of 10 sec at 20 minute intervals for a total of 5 doses. This dose is a projection to produce a prominent vascular response and will be confirmed during actual experiments. Arterial and pulmonary arterial blood pressure responses to each dose will be monitored continuously. Also to be monitored will be lead II EKG and heart rate. Expanded polygraph recordings (10 sec) will be obtained before and at the point of the greatest vascular response.

Venous blood samples (5 ml) will be taken 1 minute prior to each injection and just prior to the nadir of the depressor response and held in ice. Following rapid separation in a cooled centrifuge, and pH of the plasma (2 ml) will be adjusted to 4-5 with a small volume (~ 100 µl) of 2.0 M HCl, mixed, and frozen until analysis for histamine. Plasma will be shipped frozen to Burroughs-Wellcome for this analysis.

These beagles will be allowed to recover from the anesthesia and used for a subsequent experiment. A possible secondary experiment, if results of the primary experiment warrant, would be assessment of the effect of histamine receptor blockade (H1 and H2) with chlorpheniramine and cimetidine on the vascular responses to liposome carrier.

Closing note: An alternative or concurrent consideration is the use of the specific histamine-depleting agent, Compound #48/80. We might determine if repeated i.v. administration of this compound with subsequent tachyphalaxis to its hypotensive response yields a preparation which is then unresponsive to liposome carrier.

Robert W. Caldwell, Ph.D.

Clinton B. Nash, Ph.D.

RWC:sbu

SECTION III.

Effects of Carrier Liposomes on the Canine Cardiovascular System.

Methods

Four dogs screened for parasites, in good general health and weighing between 9.6 and 11.2 kg were anesthetized with Na-pentobarbital (30 mg/kg, i.v.) and maintained with doses of 1 to 2 mg/kg as necessary. (See Protocol -- Cardiovascular and Pulmonary Effects of WR-6026•2HCl vs Primaquine•$2H_3PO_4$.) Two dogs received a test liposome infusion (.3 ml/min for 15 min) via femoral vein with no prior treatment and two dogs received a liposome infusion (.3 ml/min for 15 min) 30 minutes after pretreatment with a symmetrical disulfide WR-149,024 (10 mg/kg, i.v.) The carrier Liposome suspension and WR-149,024 used were furnished by WRAIR. Dogs were fitted with tracheal cannulae and breathed room air. Central aortic blood pressure was measured via left carotid artery using a Statham pressure transducer. Central venous pressure was measured via right external jugular vein using a Gould transducer. Lead II EKG and heart rate were measured continously using a Grass EKG pre-amplifier and tachometer preamplifier, respectively. Limb EKG leads were recorded at 15 min intervals. A Grass polygraph was used to record all cardiovascular variables. Arterial and venous blood samples were drawn through aforementioned cannulae (carotid and jugular) at 0, +15, +30, +60, +90, and +120 minutes. Six ml of arterial blood and four ml of venous blood were drawn into glass syringes rinsed with Na-heparin. Two ml arterial blood were used for duplicate macrohematocrit (Weintraub). Samples were centrifuged immediately after being drawn and plasma was frozen immediately after centrifugation and stored for future analysis. Variables were measured for 120 minutes from onset of the infusion.

Presentation of Data

Central aortic diastolic blood pressure is expressed as percent of baseline value, with baseline as the value at time zero and equal to 100%. Central venous pressure is expressed as mean values in mmHg. Systolic arterial pressure and pulse pressure are also expressed in mmHg. Heart rate is expressed as beats/min and macrohematocrit is expressed as %cells. All pressure and heart rate values are shown as graphs and/or in tabular form. Macrohematocrit is shown in tabular form. Lead II EKG tracing at 0, +15 and +120 minutes are included for each experiment.

Results

Infusion of liposome with no pretreatment produced a transient depression of diastolic aortic pressure (see fig. and Table 1). In one animal (6/18/84), the decline in pressure was gradual and fairly uniform during the infusion and shortly thereafter. Fifteen minutes after the infusion was over pressure began to return to its original level. In the other dog given only the liposome test dose (6/1/84), there was a sudden and sharp decrease in blood pressure (within 2.5 min) followed by a sharp rise (+5 min); blood pressure then returned to baseline value (10 min) and stayed within ±10% of baseline until near the end of the experiment (+90 min) when there was a further, but slight drop.

Administration of WR-149,024 caused an immediate and marked decline in diastolic blood pressure in one dog (6/6/84) and almost no apparent effect in the other (6/19/84) (see fig. 2 and Table 1). In the animal which exhibitied this marked response to WR-149,024 (6/6/84), infusion of liposome solution had a minimal effect. Diastolic blood pressure fell only slightly towards the end of the experiment on 6/19/84.

Systolic aortic pressure was affected similarly to diastolic pressure in each dog. There was a trend, however, for it to drop more than diastolic pressure during the liposome infusion; pulse pressure was diminished slightly during liposome infusion.

Central venous pressure (CVP) fluctuated during the liposome infusions in dogs which had no pretreatment. After the infusion, one animal's CVP rose (6/19/84) and the other's fell (6/1/84), but neither by a great amount. Central venous pressure was not apparently affected by liposome infusion pretreated with WR-149,024 (6/6/84) and 6/19/84) (see fig. 2 and Table 1).

Administration of WR-149,024 caused a slight, temporary increase in heart rate (see fig. 3 and Table 1) but liposome infusion did not affect any of the animals' heart rates to a significant degree.

EKG records (Lead II) showed no change due to infusion of the Liposome suspension (see fig. 4).

Conclusions

The liposome suspension produces an arterial hypotension when given intravenously. Prior treatment with WR-149,024 appeared to reduce the development of hypotension to liposome infusion. Since one of the reported properties of WR-149,024 is to stabilize histamine-containing cells and antagonize factors which induce histamine release, we may speculate that histamine is involved in this hypotension.

Robert W. Caldwell, Ph.D.
Professor

RWC/ci

FIGURE 1

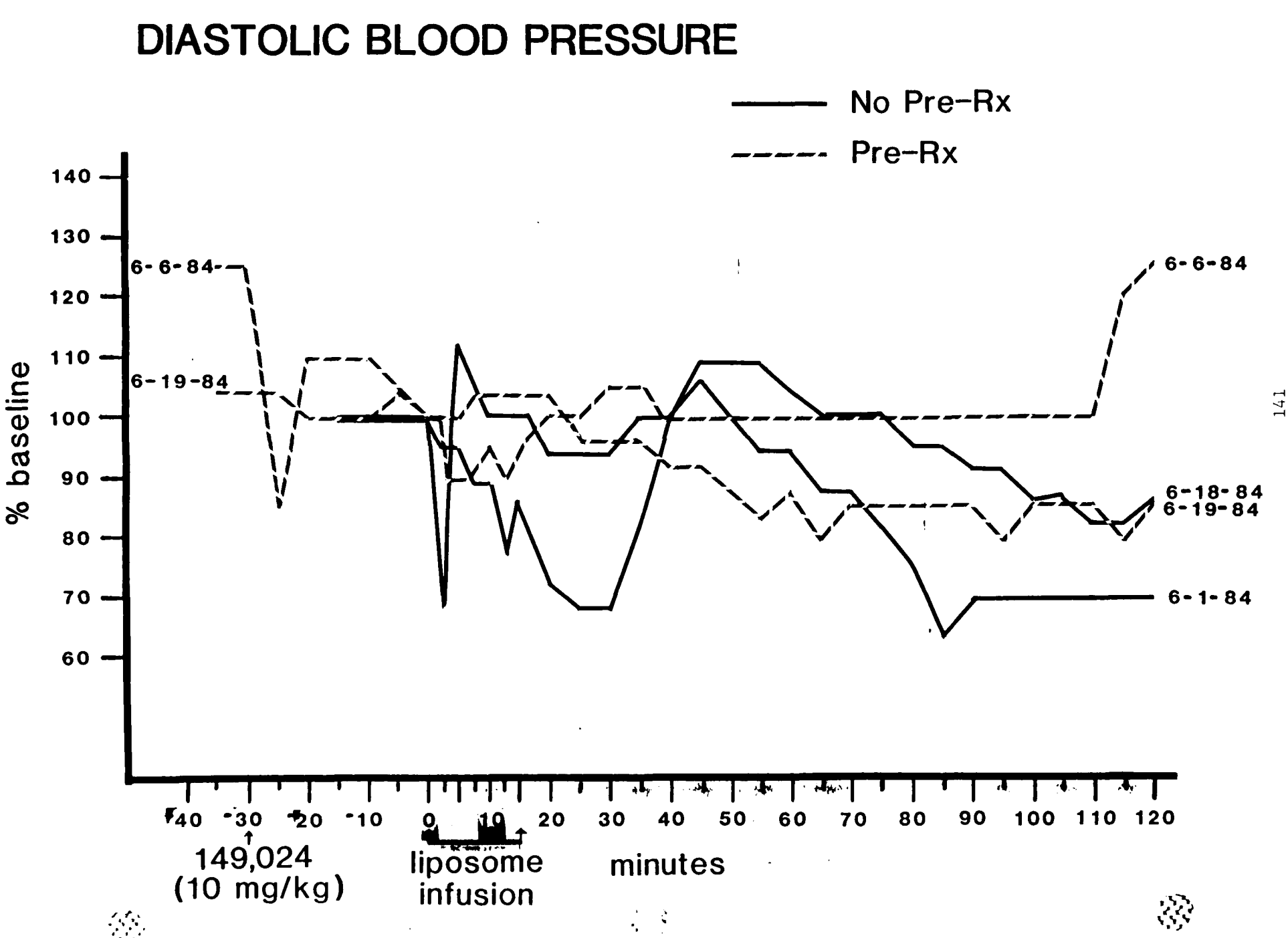
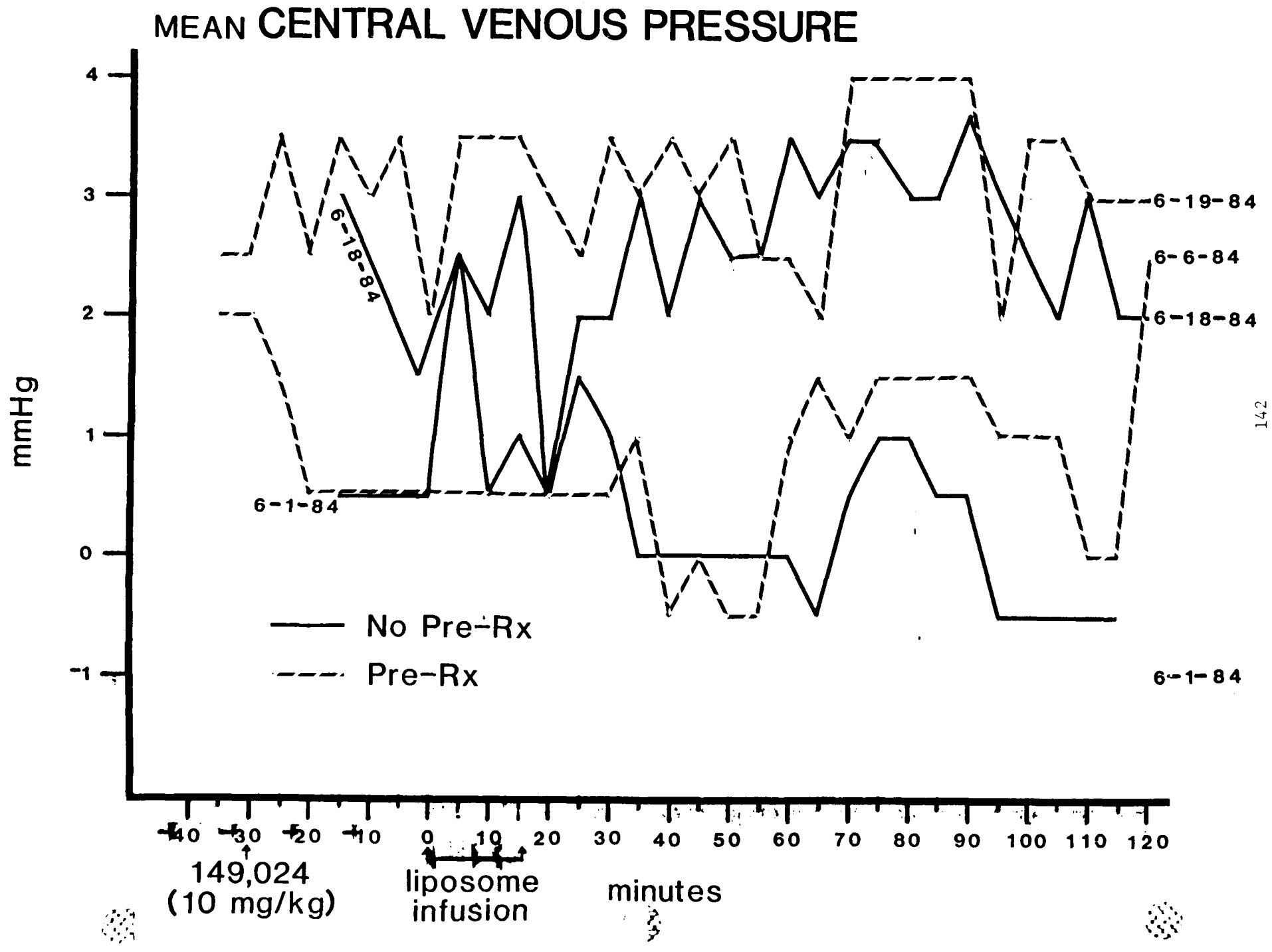

DIASTOLIC BLOOD PRESSURE
No Pre-Rx
Pre-Rx
% baseline
140
130
120
110
100
90
80
70
60
6-6-84
6-19-84
6-6-84
6-18-84
6-19-84
6-1-84
-40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100 110 120
149,024
(10 mg/kg)
liposome
infusion
minutes

FIGURE 2


MEAN CENTRAL VENOUS PRESSURE
mmHg
4
3
2
1
0
-1
6-18-84
6-1-84
6-19-84
6-6-84
6-18-84
6-1-84
No Pre-Rx
Pre-Rx
-40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100 110 120
149,024
(10 mg/kg)
liposome
infusion
minutes

142

FIGURE 3

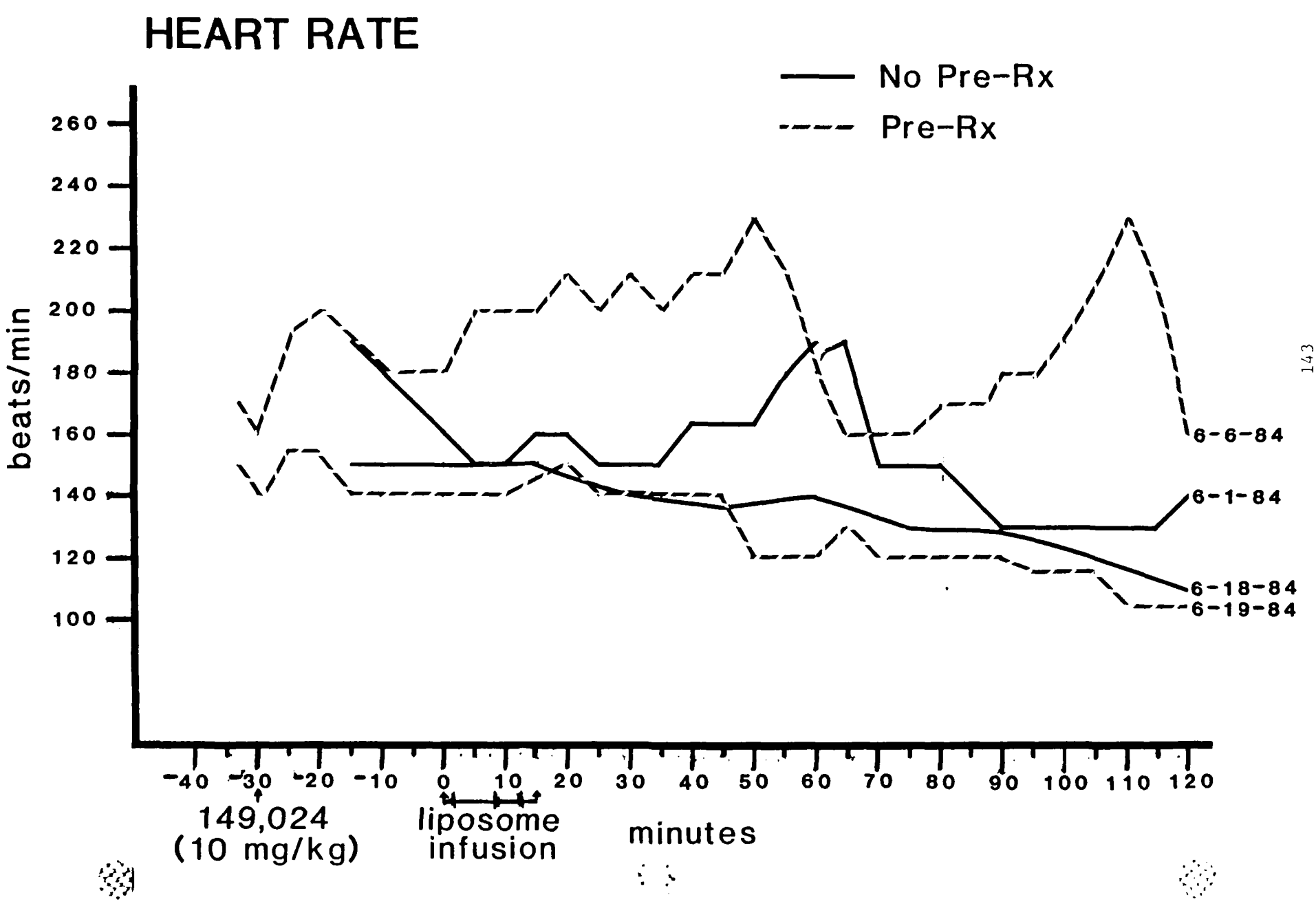
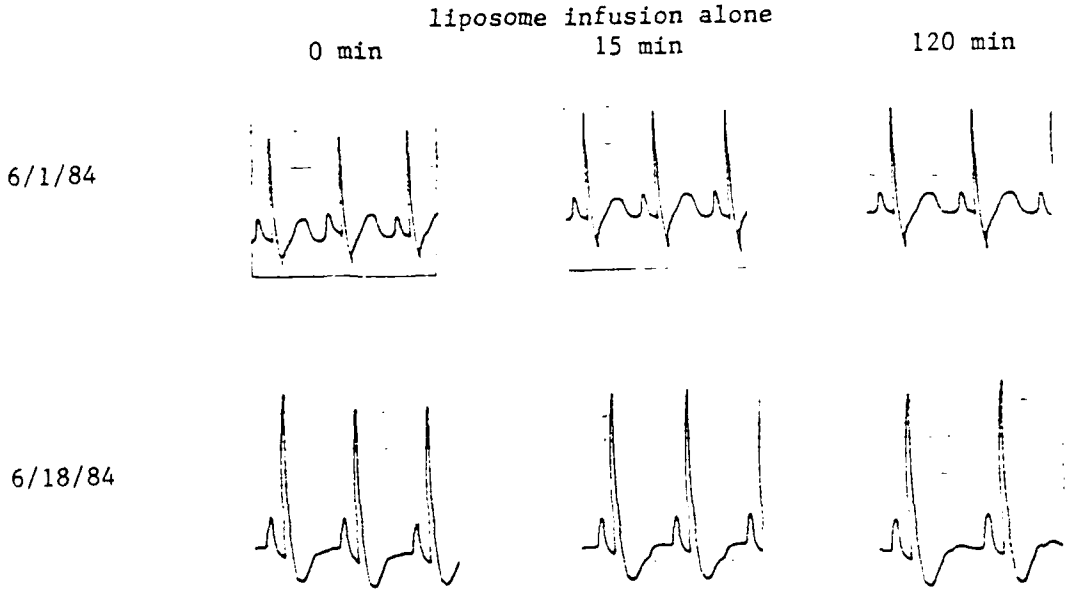

HEART RATE
No Pre-Rx
Pre-Rx
beats/min
260
240
220
200
180
160
140
120
100
6-6-84
6-1-84
6-18-84
6-19-84
-40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100 110 120
149,024
(10 mg/kg)
liposome
infusion
minutes

fig.4

Lead II EKG

liposome infusion alone



liposome infusion and pretreatment with 149,024

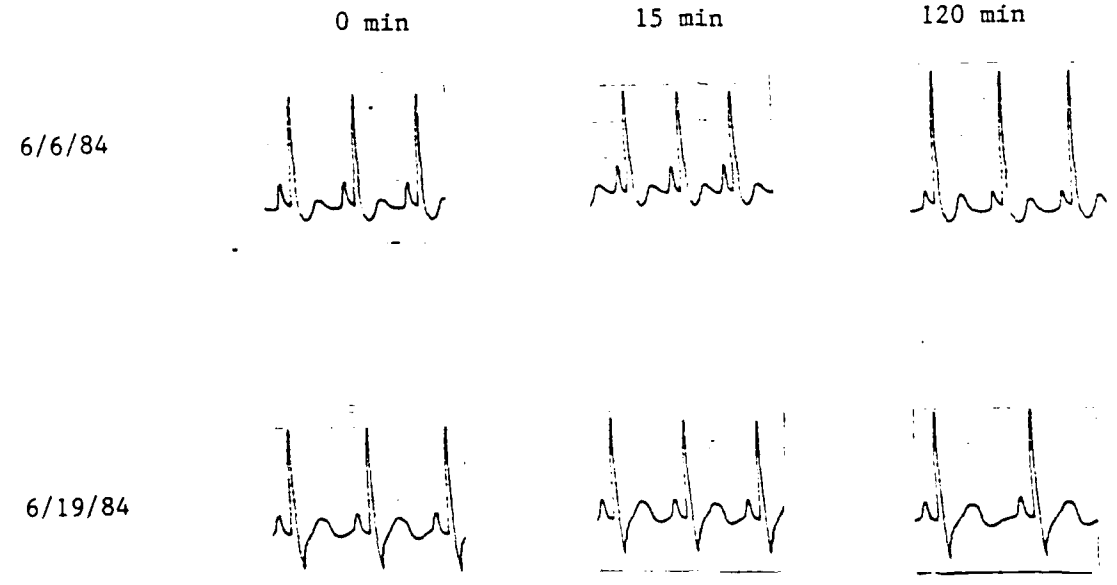


TABLE 1

	6/1/84				6/18/84				6/6/84				6/19/84			
Minutes	DBP % baseline	CVP cm Hg	HR beats/min	macro-Hct % cells	DBP % baseline	CVP mm Hg	HR beats/min	macro-Hct % cells	DBP % baseline	CVP mm Hg	HR beats/min	macro-Hct % cells	DBP % baseline	CVP mm Hg	HR beats/min	macro-Hct % cells
-35				10.0 kg				11.2 kg	125	2.0	170	9.3 kg	104.17	2.5	150	12.4 kg
-30									▲ 125	2.0	160		▲ 104.17	2.5	140	
-25									85	1.5	190		104.17	3.5	155	
-20									110	0.5	200		100	2.5	155	
-15	100	0.5	190		100	3.0	150						100	3.5	140	
-10									110	0.5	180		100	3.0	140	
0	100	0.5	160	28.5	100	1.5	150	48	100	0.5	180	44.5	100	2.0	140	38.5
2.5	68.75				95.45				100				100			
5	112.5	2.5	150		95.45	2.5			90	0.5	200		100	3.5	140	
7.5	105				61.82				90				104.17			
10	* 100	0.5	150		* 61.82	2.0			* 95	0.5	200		* 104.17	3.5	140	
12.5					77.27				100				104.17			
15	100	1.0	160	26	86.36	3.0	150	49	95	0.5	200	44	104.17	3.5	145	40
20	93.75	0.5			72.73	0.5			100	0.5	210		104.17	3.0	150	
25	93.75	1.5	150		68.18	2.0			100	0.5	200		95.93	2.5	140	
30	93.75	1.0	150	25	68.18	2.0	140	47.5	105	0.5	210	44.5	95.93	3.5	140	41.75
35	100	0	150		81.82	2.0			105	1.0	200		95.93	3.0	140	
40	100	0	160		100	2.0			100	-0.5	210		91.67	3.5	140	
45	106.25	0	160		109.09	3.0	135		100	0	210		91.67	3.0	140	
50	100	0	160		109.09	2.5			100	-0.5	250		87.50	3.5	120	
55	93.76	0	180		109.09	2.5			100	-0.5	210		83.33	2.5	120	
60	93.75	0	140	27	104.54	3.5	140	49	100	1.0	180	52	87.50	2.5	120	45.25
65	87.5	-0.5	140		100	3.0			100	1.5	160		79.17	2.0	130	
70	87.5	0.5	150		100	3.5			100	1.0	160		83.33	4.0	120	
75	81.25	1.0	150		100	3.5	130		100	1.5	160		83.33	4.0	120	
80	75.0	1.0	150		95.45	3.0			100	1.5	170		83.33	4.0	120	
85	62.5	0.5	140		95.45	3.0			100	1.5	170		83.33	4.0	120	
90	68.75	0.5	130	26.5	90.91	3.7	130	52.5	100	1.5	180	57	83.33	4.0	120	44
95	68.75	-0.5	130		90.91	3.0			100	1.0	180		79.17	2.0	115	
100	68.75	-0.5	130		86.36	2.5			100	1.0	190		83.33	3.5	115	
105	68.75	-0.5	130		86.36	2.0	120		100	1.0	210		83.33	3.5	115	
110	68.75	-0.5	130		81.82	3.0			100	0	230		83.33	3.0	105	
115	68.75	-0.5	130		81.82	2.0			120	0	210		79.17	3.0	105	
120	68.75	-1.0	140	27	86.36	2.0	110	51	125	0.5	160	57.5	83.33	3.0	105	44.5

* Liposome infusion (i.v.) from 0 to +15 minutes

▲ Pre-Rx with WR-149,024 at 10 mg/kg (i.v.)

TABLE 2

Minutes	6/11/84 ABP mm Hg	Pulse pressure mm Hg	6/18/84 ABP mm Hg	Pulse pressure mm Hg	6/6/84 ABP mm Hg	Pulse pressure mm Hg	6/19/84 ABP mm Hg	Pulse pressure mm Hg
-35					175/125	50	165/125	40
-30					▲ 175/125	50	▲ 165/125	40
-25					120/85	35	150/115	35
-20					160/110	50	153/120	35
-15	110/80	30	160/110	50			155/120	35
-10					160/110	50	160/120	40
0	105/80	25	165/110	55	145/100	45	160/120	40
2.5	* 80/55	25	* 155/105	50	* 135/100	35	* 124/120	40
5	110/90	20	150/105	45	135/90	45	160/120	40
7.5	105/85	20	135/90	45	125/90	35	160/125	35
10	100/80	20	130/90	40	130/85	35	160/125	35
12.5	100/80	20	125/85	40	135/100	35	160/125	35
15	100/80	20	135/95	45	135/95	40	160/125	35
20	100/75	25	135/80	55	135/100	35	160/125	35
25	100/75	25	140/75	65	140/100	40	155/115	40
30	100/75	25	140/75	65	145/105	40	150/115	35
35	105/80	25	140/90	50	140/105	35	150/115	35
40	105/80	25	150/110	40	145/100	45	150/110	40
45	110/85	25	155/120	35	140/100	40	145/110	35
50	115/80	35	155/120	35	145/100	45	145/105	40
55	120/75	45	155/120	35	150/100	50	130/100	30
60	120/75	45	155/115	40	160/100	60	140/105	35
65	110/70	40	155/110	45	150/100	50	125/95	30
70	105/70	35	155/110	45	150/100	50	130/100	30
75	100/65	35	160/110	50	145/100	45	130/100	30
80	95/60	35	155/105	50	145/100	45	125/100	25
85	90/50	40	155/105	50	140/100	40	125/100	25
90	90/55	35	150/100	50	140/100	40	125/100	25
95	95/55	40	150/100	50	135/100	35	120/95	25
100	95/55	40	145/95	50	140/100	40	125/100	25
105	90/55	35	145/95	50	140/100	40	125/100	25
110	95/55	40	135/90	45	140/100	40	120/100	20
115	90/55	35	140/90	50	155/120	35	125/95	30
120	90/55	35	141/95	45	170/125	45	125/100	25

* liposome infusion (0 to +15 min)

▲ Pre-Rx with WR-149,024 @ 10 mg/kg (i.v.)

ABP = arterial blood pressure

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